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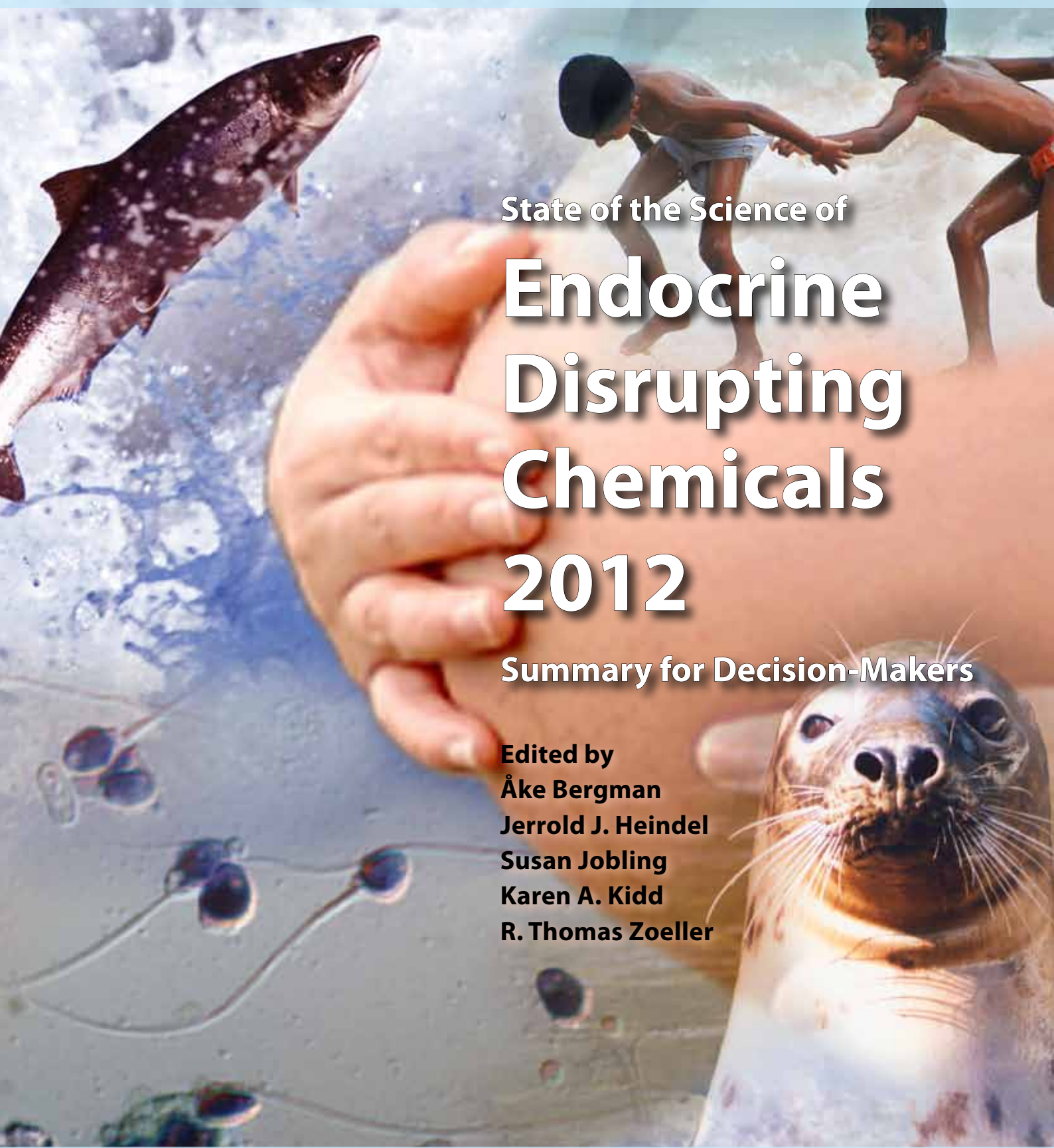

State of the Science of

Endocrine Disrupting Chemicals 2012

Summary for Decision-Makers

Edited by
Åke Bergman
Jerrold J. Heindel
Susan Jobling
Karen A. Kidd
R. Thomas Zoeller

IOMC INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS

A cooperative agreement among **FAO, ILO, UNDP, UNEP, UNIDO, UNITAR, WHO, World Bank and OECD**

This publication was developed in the IOMC context. The contents do not necessarily reflect the views or stated policies of individual IOMC Participating Organizations.

The Inter-Organisation Programme for the Sound Management of Chemicals (IOMC) was established in 1995 following recommendations made by the 1992 UN Conference on Environment and Development to strengthen co-operation and increase international co-ordination in the field of chemical safety. The Participating Organisations are FAO, ILO, UNDP, UNEP, UNIDO, UNITAR, WHO, World Bank and OECD. The purpose of the IOMC is to promote co-ordination of the policies and activities pursued by the Participating Organisations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

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State of the Science of

Endocrine Disrupting Chemicals 2012

Summary for Decision-Makers

An assessment of the state
of the science of endocrine disruptors
prepared by a group of experts
for the United Nations Environment Programme
and World Health Organization.

Edited by
Åke Bergman
Jerrold J. Heindel
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World Health Organization

UNEP

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1972-2012:
Serving People
and the Planet

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Preface

This *Summary for Decision-Makers*, together with the main document, *State of the Science of Endocrine Disrupting Chemicals—2012*, presents information and key concerns for policy-makers on endocrine disruptors as part of the ongoing collaboration between the World Health Organization (WHO) and the United Nations Environment Programme (UNEP) to address concerns about the potential adverse health effects of chemicals on humans and wildlife. The main messages from the three chapters of the main document are presented as well.

We live in a world in which man-made chemicals have become a part of everyday life. It is clear that some of these chemical pollutants can affect the endocrine (hormonal) system, and certain of these endocrine disruptors may also interfere with the developmental processes of humans and wildlife species. Following international recommendations in 1997 by the Intergovernmental Forum on Chemical Safety and the Environment Leaders of the Eight regarding the issue of endocrine disrupting chemicals (EDCs), WHO, through the International Programme on Chemical Safety (IPCS), a joint programme of WHO, UNEP and the International Labour Organization, developed in 2002 a report entitled *Global Assessment of the State-of-the-Science of Endocrine Disruptors*.

The Strategic Approach to International Chemicals Management (SAICM) was established by the International Conference on Chemicals Management (ICCM) in February 2006, with the overall objective to achieve the sound management of chemicals throughout their life cycle so that, by 2020, chemicals are used and produced in ways that minimize significant adverse effects on human health and the environment.

SAICM recognizes that risk reduction measures need to be improved to prevent the adverse effects of chemicals on the health of children, pregnant women, fertile populations, the elderly, the poor, workers and other vulnerable groups and susceptible environments. It states that one measure to safeguard the health of women and children is the minimization of chemical exposures before conception and through gestation, infancy, childhood and adolescence.

SAICM also specifies that groups of chemicals that might be prioritized for assessment and related studies, such as for the development and use of safe and effective alternatives, include chemicals that adversely affect, inter alia, the reproductive, endocrine, immune or nervous systems. A resolution to include EDCs as an emerging issue under SAICM was adopted in September 2012 by ICCM at its third session.

EDCs represent a challenge, as their effects depend on both the level and timing of exposure, being especially critical when exposure occurs during development. They have diverse applications, such as pesticides, flame retardants in different products, plastic additives and cosmetics, which may result in residues or contaminants in food and other products. Therefore, EDCs may be released from the products that contain them.

The protection of the most vulnerable populations from environmental threats is a key component of the Millennium Development Goals. As the challenge in meeting the existing goals increases, with work under way in developing countries to overcome traditional environmental threats while dealing with poverty, malnutrition and infectious disease, emerging issues should be prevented from becoming future traditional environmental threats. Endocrine disruption is a challenge that must continue to be addressed in ways that take into account advances in our knowledge.

UNEP and WHO, in collaboration with a working group of international experts, are taking a step forward by developing these documents on endocrine disruptors, including scientific information on their impacts on human and wildlife health and key concerns for decision-makers and others concerned. The well-being of future human and wildlife generations depends on safe environments.

From late 2010 until mid-2012, the working group developed, contributed to and revised sections of the main document during three separate meetings, as well as through teleconferences. Professor Åke Bergman led the working group and facilitated the development of this summary with the editors in coordination with the working group, UNEP and WHO.

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The working group members, scientific experts and contributors of text served as individual scientists and not as representatives of any organization, government or industry. All individuals who participated in the preparation of these documents served in their personal capacity and were required to sign a Declaration of Interest statement informing the Responsible Officer if, at any time, there was a conflict of interest perceived in their work. Such a procedure was followed, and no conflicts of interest were identified.

The development and publication of the two documents were supported by funds provided to UNEP by the Norwegian government, the Swedish Environment Ministry, the Swedish Research Council (FORMAS) and the Swedish Environmental Protection Agency. Further support was provided to WHO by the United States National Institute of Environmental Health Sciences (NIEHS) through cooperative agreement 1 U01 ES02617. The contents of the documents are solely the responsibility of the contributors and do not necessarily represent the official views of the NIEHS.

1. Introduction

This document presents summary information and key concerns for decision-makers on endocrine disrupting chemicals (EDCs) from the full report entitled *State of the Science of Endocrine Disrupting Chemicals—2012*. It is part of the ongoing collaboration between the United Nations Environment Programme (UNEP) and the World Health Organization (WHO) to address concerns about the potential adverse effects of anthropogenic chemicals.

We live in a world in which man-made chemicals have become a part of everyday life. Some of these chemical pollutants can affect the endocrine (hormonal) system and interfere with important developmental processes in humans and wildlife.

Following international recommendations in 1997 by the Intergovernmental Forum on Chemical Safety and the Environment Leaders of the Eight regarding the issue of EDCs, the International Programme on Chemical Safety (IPCS), a joint programme of WHO, UNEP and the International Labour Organization, developed in 2002 a report entitled *Global Assessment of the State-of-the-Science of Endocrine Disruptors* (**Figure 1**) (IPCS, 2002).

The general conclusions from this work were that

> *although it is clear that certain environmental chemicals can interfere with normal hormonal processes, there is weak evidence that human health has been adversely affected by exposure to endocrine-active chemicals. However, there is sufficient evidence to conclude that adverse endocrine-mediated effects have occurred in some wildlife species. Laboratory studies support these conclusions.*

The IPCS (2002) document further concluded that there was a need for broad, collaborative and international research initiatives and presented a list of research needs.

Since 2002, intensive scientific work has improved our understanding of the impacts of EDCs on human and wildlife health. Recent scientific reviews and reports published by the Endocrine Society (Diamanti-Kandarakis et al., 2009), the European Commission (Kortenkamp et al., 2011) and the European Environment Agency (2012) illustrate the scientific interest in and complexity of this issue. These documents concluded that there is emerging evidence for adverse reproductive outcomes (infertility, cancers, malformations) from exposure to EDCs, and there is also mounting evidence for effects of these chemicals on thyroid function, brain function, obesity and metabolism, and insulin and glucose homeostasis.

The Endocrine Society called for timely action to prevent harm (Diamanti-Kandarakis et al., 2009), and the European Society for Paediatric Endocrinology and the Pediatric Endocrine Society, based in the United States of America (USA), put forward a consensus statement calling for action regarding endocrine disruptors and their effects (Skakkebaek et al., 2011).

In 2012, UNEP and WHO, in collaboration with international experts, have taken a step forward by supporting the development of a main document on endocrine disruptors, including scientific information on their impacts on human and wildlife health, scientific developments over the decade since publication of the IPCS (2002) report and key concerns. The collaboration also included the development of the present summary report, which is aimed at decision-makers and others concerned about the future of human and wildlife health. The key concerns and main messages from the three chapters of the main document are also presented in this summary.

The main document provides an assessment of the strength of the evidence supporting the hypothesis that chemicals with endocrine activity are a causal factor in the manifestation of specific conditions.

The *State of the Science of Endocrine Disrupting Chemicals—2012* report starts by explaining what endocrine disruption is all about and then reviews our current knowledge of endocrine disrupting effects in humans and in wildlife. The document ends with a review of sources of and exposures to EDCs. The present *Summary for Decision-Makers* refers to the detailed information, including references, given in the main report (UNEP/WHO, 2012).

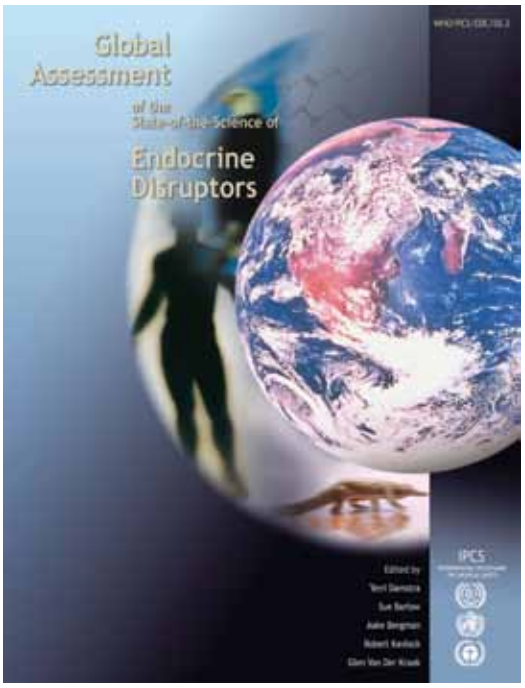


Figure 1. The *Global Assessment of the State-of-the-Science of Endocrine Disruptors* report, as published by IPCS in 2002.

2. Key concerns

- **Human and wildlife health depends on the ability to reproduce and develop normally. This is not possible without a healthy endocrine system.**
- **Three strands of evidence fuel concerns over endocrine disruptors:**
  - The high incidence and the increasing trends of many endocrine-related disorders in humans;
  - Observations of endocrine-related effects in wildlife populations;
  - The identification of chemicals with endocrine disrupting properties linked to disease outcomes in laboratory studies.
- **Many endocrine-related diseases and disorders are on the rise.**
  - Large proportions (up to 40%) of young men in some countries have low semen quality, which reduces their ability to father children.
  - The incidence of genital malformations, such as non-descending testes (cryptorchidisms) and penile malformations (hypospadias), in baby boys has increased over time or levelled off at unfavourably high rates.
  - The incidence of adverse pregnancy outcomes, such as preterm birth and low birth weight, has increased in many countries.
  - Neurobehavioural disorders associated with thyroid disruption affect a high proportion of children in some countries and have increased over past decades.
  - Global rates of endocrine-related cancers (breast, endometrial, ovarian, prostate, testicular and thyroid) have been increasing over the past 40–50 years.
  - There is a trend towards earlier onset of breast development in young girls in all countries where this has been studied. This is a risk factor for breast cancer.
  - The prevalence of obesity and type 2 diabetes has dramatically increased worldwide over the last 40 years. WHO estimates that 1.5 billion adults worldwide are overweight or obese and that the number with type 2 diabetes increased from 153 million to 347 million between 1980 and 2008.
- **Close to 800 chemicals are known or suspected to be capable of interfering with hormone receptors, hormone synthesis or hormone conversion. However, only a small fraction of these chemicals have been investigated in tests capable of identifying overt endocrine effects in intact organisms.**
  - The vast majority of chemicals in current commercial use have not been tested at all.
  - This lack of data introduces significant uncertainties about the true extent of risks from chemicals that potentially could disrupt the endocrine system.
- **Human and wildlife populations all over the world are exposed to EDCs.**
  - There is global transport of many known and potential EDCs through natural processes as well as through commerce, leading to worldwide exposure.
  - Unlike 10 years ago, we now know that humans and wildlife are exposed to far more EDCs than just those that are persistent organic pollutants (POPs).
  - Levels of some newer POPs in humans and wildlife are still increasing, and there is also exposure to less persistent and less bioaccumulative, but ubiquitous, chemicals.
  - New sources of human exposure to EDCs and potential EDCs, in addition to food and drinking-water, have been identified.
  - Children can have higher exposures to chemicals compared with adults—for example, through their hand-to-mouth activity and higher metabolic rate.
- **The speed with which the increases in disease incidence have occurred in recent decades rules out genetic factors as the sole plausible explanation. Environmental and other non-genetic factors, including nutrition, age of mother, viral diseases and chemical exposures, are also at play, but are difficult to identify. Despite these difficulties, some associations have become apparent:**
  - Non-descended testes in young boys are linked with exposure to diethylstilbestrol (DES) and polybrominated diphenyl ethers (PBDEs) and with occupational pesticide exposure during pregnancy. Recent evidence also shows links with the painkiller paracetamol. However, there is little to suggest that polychlorinated biphenyls (PCBs) or dichlorodiphenyldichloroethylene (DDE) and dichlorodiphenyltrichloroethane (DDT) are associated with cryptorchidism.
  - High exposures to polychlorinated dioxins and certain PCBs (in women who lack some detoxifying enzymes) are risk factors in breast cancer. Although exposure to natural and synthetic estrogens is associated with breast cancer, similar evidence linking estrogenic environmental chemicals with the disease is not available.
  - Prostate cancer risks are related to occupational exposures to pesticides (of an unidentified nature), to some PCBs and to arsenic. Cadmium exposure has been linked with prostate cancer in some, but not all, epidemiological studies, although the associations are weak.

- Developmental neurotoxicity with negative impacts on brain development is linked with PCBs. Attention deficit/hyperactivity disorder (ADHD) is overrepresented in populations with elevated exposure to organophosphate pesticides. Other chemicals have not been investigated.
- An excess risk of thyroid cancer was observed among pesticide applicators and their wives, although the nature of the pesticides involved was not defined.

- **Significant knowledge gaps exist as to associations between exposures to EDCs and other endocrine diseases, as follows:**
  - There is very little epidemiological evidence to link EDC exposure with adverse pregnancy outcomes, early onset of breast development, obesity or diabetes.
  - There is almost no information about associations between EDC exposure and endometrial or ovarian cancer.
  - High accidental exposures to PCBs during fetal development or to dioxins in childhood increase the risk of reduced semen quality in adulthood. With the exception of these studies, there are no data sets that include information about fetal EDC exposures and adult measures of semen quality.
  - No studies exist that explore the potential link between fetal exposure to EDCs and the risk of testicular cancer occurring 20–40 years later.
- **Numerous laboratory studies support the idea that chemical exposures contribute to endocrine disorders in humans and wildlife. The most sensitive window of exposure to EDCs is during critical periods of development, such as during fetal development and puberty.**
  - Developmental exposures can cause changes that, while not evident as birth defects, can induce permanent changes that lead to increased incidence of diseases throughout life.
  - These insights from endocrine disruptor research in animals have an impact on current practice in toxicological testing and screening. Instead of solely studying effects of exposures in adulthood, the effects of exposures during sensitive windows in fetal development, perinatal life, childhood and puberty require careful scrutiny.
- **Worldwide, there has been a failure to adequately address the underlying environmental causes of trends in endocrine diseases and disorders.**
  - Health-care systems do not have mechanisms in place to address the contribution of environmental risk factors to endocrine disorders. The benefits that can be reaped by adopting primary preventive measures for dealing with these diseases and disorders have remained largely unrealized.
- **Wildlife populations have been affected by endocrine disruption, with negative impacts on growth and reproduction. These effects are widespread and have been due primarily to POPs. Bans of these chemicals have reduced exposure and led to recovery of some populations.**
  - It is therefore plausible that additional EDCs, which have been increasing in the environment and are of recent concern, are contributing to current population declines in wildlife species. Wildlife populations that are also challenged by other environmental stressors are particularly vulnerable to EDC exposures.
- **Internationally agreed and validated test methods for the identification of endocrine disruptors capture only a limited range of the known spectrum of endocrine disrupting effects. This increases the likelihood that harmful effects in humans and wildlife are being overlooked.**
  - For many endocrine disrupting effects, agreed and validated test methods do not exist, although scientific tools and laboratory methods are available.
  - For a large range of human health effects, such as female reproductive disorders and hormonal cancers, there are no viable laboratory models. This seriously hampers progress in understanding the full scale of risks.
- **Disease risk due to EDCs may be significantly underestimated.**
  - A focus on linking one EDC to one disease severely underestimates the disease risk from mixtures of EDCs. We know that humans and wildlife are simultaneously exposed to many EDCs; thus, the measurement of the linkage between exposure to mixtures of EDCs and disease or dysfunction is more physiologically relevant. In addition, it is likely that exposure to a single EDC may cause disease syndromes or multiple diseases, an area that has not been adequately studied.
- **An important focus should be on reducing exposures by a variety of mechanisms. Government actions to reduce exposures, while limited, have proven to be effective in specific cases (e.g. bans and restrictions on lead, chlorpyrifos, tributyltin, PCBs and some other POPs). This has contributed to decreases in the frequency of disorders in humans and wildlife.**
- **Despite substantial advances in our understanding of EDCs, uncertainties and knowledge gaps still exist that are too important to ignore. These knowledge gaps hamper progress towards better protection of the public and wildlife. An integrated, coordinated international effort is needed to define the role of EDCs in current declines in human and wildlife health and in wildlife populations.**

3. Endocrine systems and endocrine disruption

For the purposes of this report, we have adopted the definition of an endocrine disruptor that was used in the IPCS (2002) document on endocrine disruptors (see textbox). Simplified, this means that endocrine disruptors are chemicals, or chemical mixtures, that interfere with normal hormone action.

To understand endocrine disruption, we must understand the basic features of the endocrine system, which consists of many interacting tissues that talk to each other and the rest of the body using signalling mediated by molecules called hormones. The human endocrine system is visualized in **Figure 2**. It is responsible for controlling a large number of processes in the body, including early processes, such as cell differentiation during development and organ formation, as well as most tissue and organ functions throughout adulthood (**Figure 3**). A hormone is a molecule produced by an endocrine gland that travels through the blood to produce effects on distant cells and tissues via integrated complex interacting signalling pathways usually involving hormone receptors. There are over 50 different hormones and hormone-related molecules (cytokines and neurotransmitters) in humans that integrate and control normal body functions across and between tissues and organs over the lifespan. This is also the case in wildlife. Hormones and their signalling pathways are critical to the normal functioning of every tissue and organ in both vertebrates and invertebrates and are often quite similar across species.

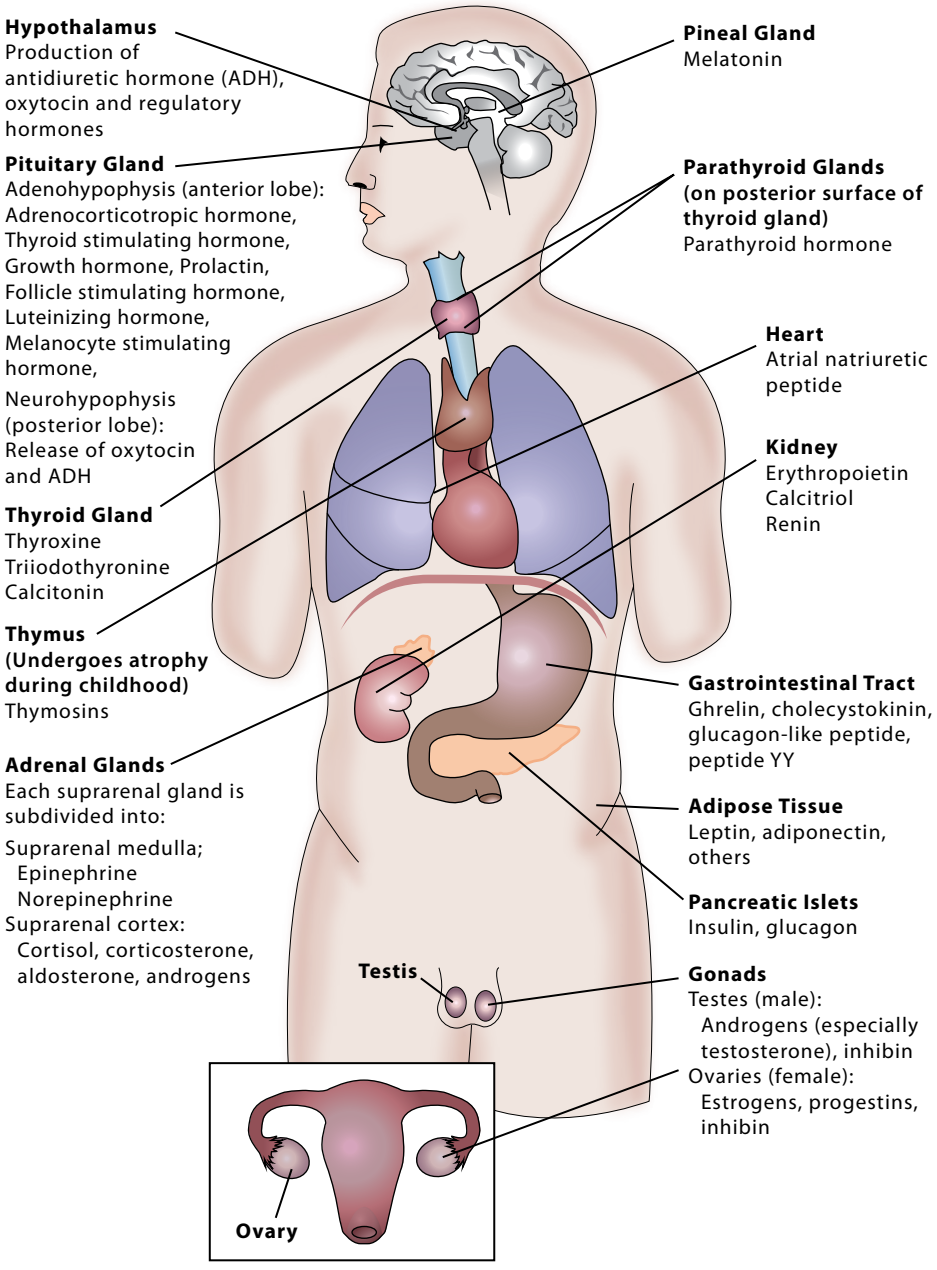


Figure 2. Overview of the endocrine system. Figure shows endocrine glands and some examples of hormones produced.

Definition of EDCs (IPCS, 2002)

*"An **endocrine disruptor** is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations."*

*"A **potential endocrine disruptor** is an exogenous substance or mixture that possesses properties that might be expected to lead to endocrine disruption in an intact organism, or its progeny, or (sub) populations."*

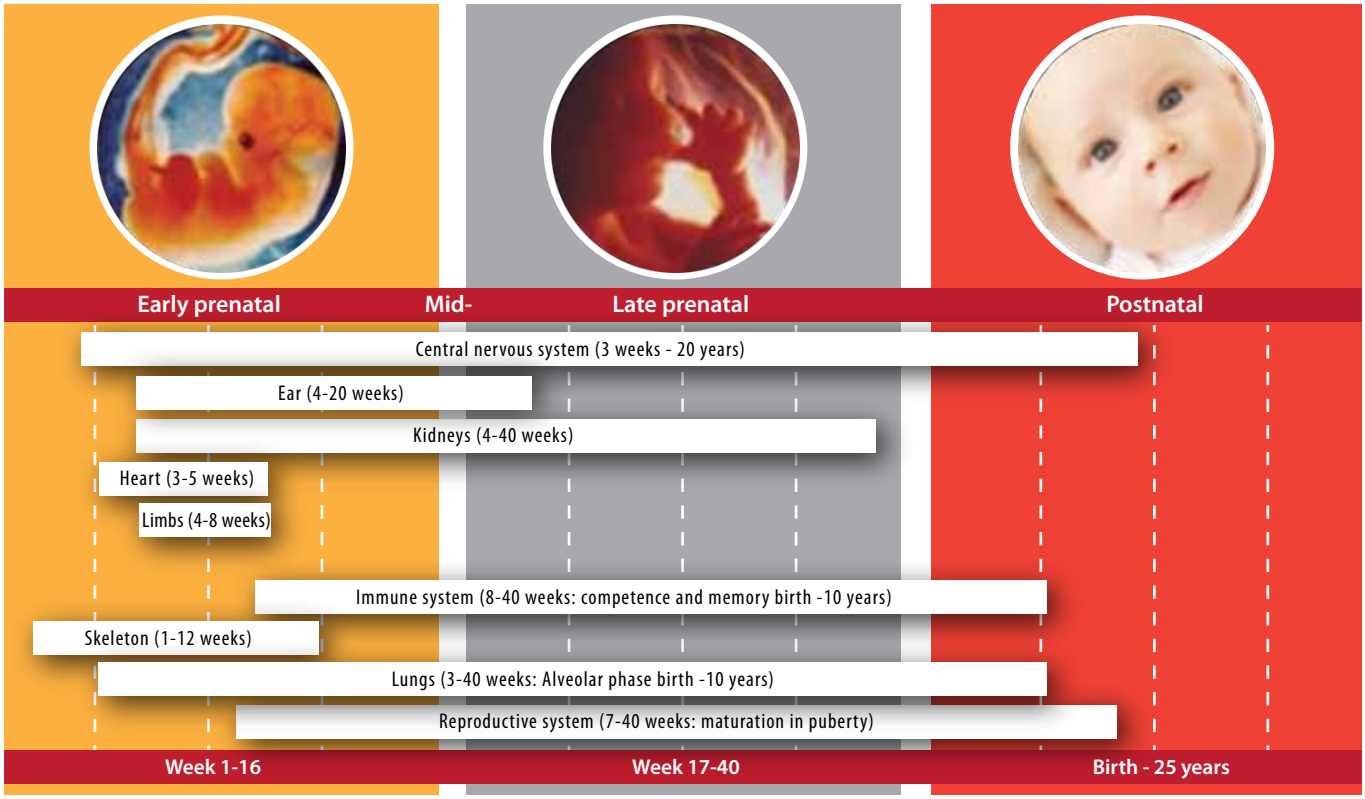


Figure 3. Sensitive windows of development. Each tissue has a specific window during development when it is forming. That is the sensitive window for effects of EDCs. Notice that some tissues continue developing after birth and into infancy and childhood, providing a longer window for exposures to affect programming.

Table 1. Comparison of hormone and endocrine disruptor action.

Hormones	Endocrine disruptors
Act via hormone receptors – Some have multiple receptors – Tissue-specific receptor classes and subtypes – Hormones normally bind similarly to all receptor subtypes	Some act via hormone receptors and multiple receptors – Will cause abnormal receptor function – Likely isoform-specific interactions
Active at low doses – Blood levels do not always reflect activity – May be bound to serum proteins in blood with a small percentage free – No bioaccumulation	Some act at low doses, others variable – Blood levels do not always reflect activity – May be bound to serum proteins – Effects on hormone blood levels may not reflect on hormone action – Possible bioaccumulation
Non-linear dose–response relationships – Always saturable with variable dynamic range – Can exhibit non-monotonic dose–response relationships – High-dose effects not same as low-dose effects	Non-linear dose–response relationships – Always saturable with variable dynamic range – Can exhibit non-monotonic dose–response relationships – High-dose effects not same as low-dose effects
Tissue-specific and life stage–specific effects	Tissue-specific and life stage–specific effects
Developmental effects permanent – Programmes brain and endocrine system for adult function	Developmental effects permanent – Interferes with programming processes
Different end-points vary in sensitivity	Different end-points vary in sensitivity

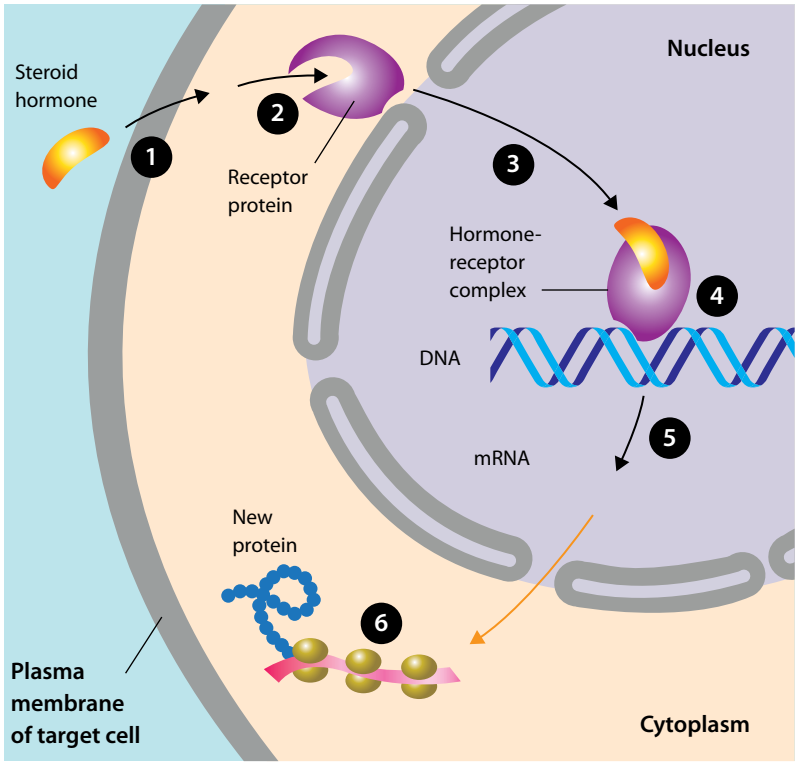


Figure 4. Example of hormone action. Many hormones act via binding to specific receptors (2) to stimulate the synthesis of new proteins (6), which then control tissue function. Some hormones also act via receptors on the membrane; in that case, the actions are more immediate in nature.

Endocrine disruptors are chemicals that interfere in some way with hormone action and in so doing can alter endocrine function such that it leads to adverse effects on human and wildlife health.

The diverse systems affected by EDCs likely include all hormonal systems and range from those controlling the development and function of reproductive organs to the tissues and organs regulating metabolism and satiety. Effects on these systems can lead to obesity, infertility or reduced fertility, learning and memory difficulties, adult-onset diabetes or cardiovascular disease, as well as a variety of other diseases. We have only recently understood that EDCs can affect the systems that control fat development and weight gain. This is a good example of complex physiological systems that are influenced by EDCs that were not known just a few years ago. Generally, there are two pathways by which a chemical could disrupt hormone action: a direct action on a hormone–receptor protein complex or a direct action on a specific protein that controls some aspect of hormone delivery to the right place at the right time (**Figure 3**). EDCs exhibit the same characteristics as hormones (**Table 1**), and they can often interfere with all processes controlled by hormones. The affinity of an endocrine disruptor for a hormone receptor is not equivalent to its potency. Chemical potency on a hormone system is dependent upon many factors.

Thus, EDCs act like hormones. Like hormones, which act via binding to receptors (**Figure 4**) at very low concentrations, EDCs have the ability to be active at low concentrations, many in the range of current human and wildlife exposures. EDCs can exert effects on more than estrogen, androgen and thyroid hormone action. Some are known to interact with multiple hormone receptors simultaneously. EDCs can work together to produce additive or synergistic effects not seen with the individual chemicals. EDCs also act on a variety of physiological processes in a tissue-specific manner and sometimes act via dose–response curves that are non-monotonic (non-linear). Indeed, as with hormones, it is often not possible to extrapolate low-dose effects from the high-dose effects of EDCs. Timing of exposures is also critical, as exposures during development likely lead to irreversible effects, whereas the effects of adult exposures seem to go away when the EDC is removed. Sensitivity to endocrine disruption is highest during tissue development. It is important that these specific characteristics of EDCs be taken into account when the toxicity of a chemical with potential EDC activity is assessed.

4. Endocrine disruptors and human health

The data linking exposures to EDCs and human diseases are much stronger now than in 2002. Since human studies can show associations only, not cause and effect, it is important to use both human and animal data to develop the evidence for a link between exposures to EDCs and human disease. Even so, it may never be possible to be absolutely certain that a specific exposure causes a specific disease or dysfunction due to the complexity of both exposures and disease etiology across the lifespan (**Figure 5**).

• Reproductive/endocrine
- Breast/prostate cancer
- Endometriosis
- Infertility
- Diabetes/metabolic syndrome
- Early puberty
- Obesity

• Immune/autoimmune
- Susceptibility to infections
- Autoimmune disease

• Cardiopulmonary
- Asthma
- Heart disease/hypertension
- Stroke

• Brain/nervous system
- Alzheimer disease
- Parkinson disease
- ADHD/learning disabilities

Figure 5. Diseases induced by exposure to EDCs during development in animal model and human studies.

Over the past 10 years, there has been a dramatic shift in focus from investigating associations between adult exposures to EDCs and disease outcomes to linking developmental exposures to disease outcomes later in life. This is now considered the most appropriate approach for most endocrine-related diseases and dysfunctions, based on data presented below (section 8). Children are the most vulnerable humans (**Figure 6**).

Together, the animal model data and human evidence support the idea that exposure to EDCs during fetal development and puberty plays a role in the increased incidences of reproductive diseases, endocrine-related cancers, behavioural and learning problems, including ADHD, infections, asthma, and perhaps obesity and diabetes in humans.

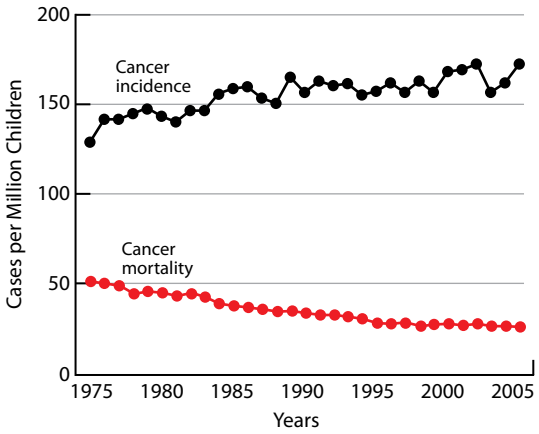


Figure 6. Children are among the most vulnerable humans. The figure shows cancer incidence and cancer mortality among children under 20 years of age in the USA (based on data from the United States National Cancer Institute's Surveillance, Epidemiology and End Results Program).

EXPOSURE TO EDCS COULD IMPAIR THE HEALTH OF OUR CHILDREN AND THEIR CHILDREN.

5. Why should we be concerned?—Human disease trends

- A significant increase in reproductive problems in some regions of the world over the last few decades points to a strong role for unidentified environmental factors in disease etiology.
- Incidences of endocrine cancers, illustrated by country or region in **Figures 7 and 8** for testicular cancer and breast cancer, respectively, have also increased during the same period.
- In certain parts of the world, there has been a significant decrease in human fertility rates, which occurred during one generation. There is also a notable rise in the use of assisted reproductive services.
- An increasing number of chemicals to which all humans in industrialized areas are exposed have been shown to interfere with hormone synthesis, action or metabolism.
- Experimental animal studies or studies with cells grown in culture have shown that many of these chemicals can also interfere with the development and function of mammalian endocrine systems.

In adults, EDC exposures have recently been linked with obesity (**Figure 9**), cardiovascular disease, diabetes and metabolic syndrome. Many of these diseases and disorders are increasing in incidence, some globally. The global health expenditure on diabetes alone was expected to a total of at least 376 billion USD in 2010 and rise to US$ 490 billion in 2030—reaching 12% of all per capita health-care expenditures (Zhang et al., 2010).

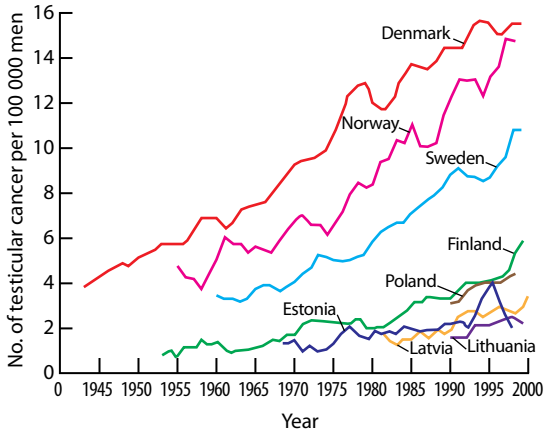


Figure 7. Testicular cancer rates across northern Europe (from Richiardi et al., 2004; used with permission of the publisher).

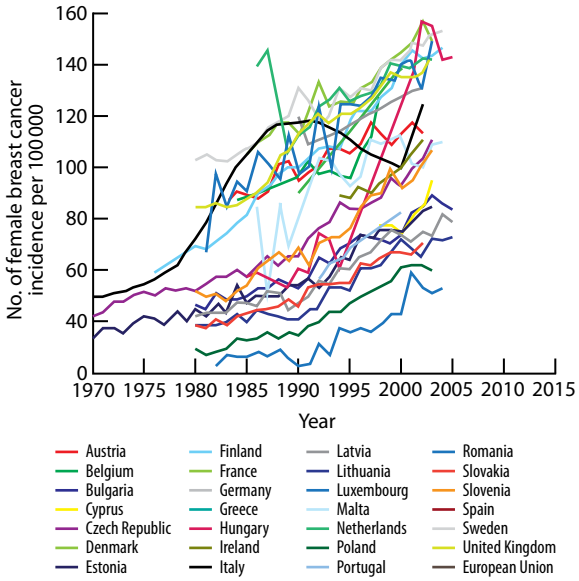


Figure 8. Female breast cancer incidence across Europe (data from http://data.euro.who.int/hfadb/).

There are other trends of concern in human paediatric health. For example, some EDCs can interact with the thyroid system in animals and humans. Normal thyroid function is very important for normal brain development, particularly during pregnancy and after birth. EDC exposures have been linked with increased rates of neurobehavioural disorders, including dyslexia, mental retardation, ADHD and autism. In many countries, these types of disorder now affect 5–10% of babies born (http://www.medscape.org/viewarticle/547415_2); autism spectrum disorders now occur at a rate that approaches 1% (http://www.cdc.gov/ncbddd/autism/addm.html).

The prevalence of paediatric asthma has more than doubled over the past 20 years and is now the leading cause of child hospitalizations and school absenteeism. Certain birth defects, such as those of the male reproductive organs (e.g. failure of the testes to descend into the scrotum), are on the rise. The incidences of paediatric leukaemia and brain cancer have risen, as has the incidence of testicular cancer. These are stark health statistics. All of these complex non-communicable diseases have both a genetic and an environmental component, and, since the increases in incidence and prevalence cannot be due solely to genetics, it is important to focus on understanding the contribution of the environment to these chronic disease trends in humans.

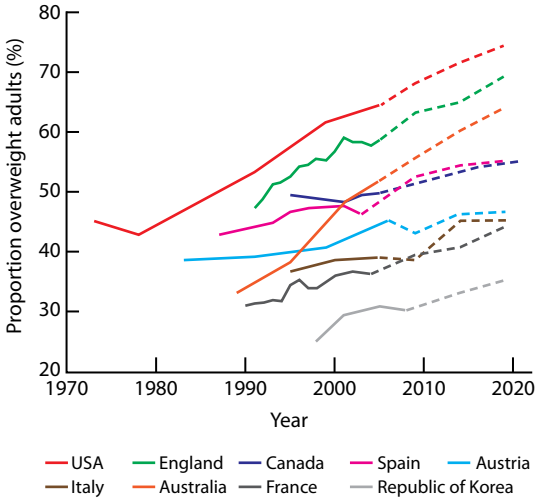


Figure 9. Past (solid lines) and projected (dashed lines) overweight rates in selected Organisation for Economic Co-operation and Development (OECD) countries.

It has been estimated that as much as 24% of human diseases and disorders are at least in part due to environmental factors (Prüss-Üstün & Corvalán, 2006). It is a challenge to identify these factors, but there is also a tremendous opportunity to improve human health by improving elements of the environment that have an impact on public health. The recognition of these challenges and opportunities, along with the fact that many of the most prevalent diseases are associated with the endocrine system, has led to a focus on EDCs.

6. Endocrine disruptors and wildlife health

Chemical exposures play a role in the deterioration of wildlife health, but understanding the role of EDCs in the global decline of populations or biodiversity is challenging. There are other natural or human-induced stressors that may confuse the picture. It is also difficult to obtain complete information about all chemicals present in the environment that might contribute to effects on wildlife. The best evidence that EDCs affect wildlife populations comes from long-term monitoring; for example, numbers of birds and molluscs are clearly increasing in regions where their exposures to chemicals (i.e. the pesticide DDT and the antifoulant tributyltin, respectively) have been reduced.

Figure 10. (right) Grey seal skull with highly eroded bone tissue associated with high POP concentrations during the 1970s and 1980s (photo by Hans Lind, used with permission).

Endocrine system function and health have been compromised in wildlife species around the world. Studies of seals in the heavily polluted Baltic Sea found very high rates of female reproductive pathologies and reproductive failure in the 1970s and 1980s, which correlated with PCB contamination. Thanks to declines in PCB pollution, these effects are uncommon today. Disturbances of the normal functioning of the thyroid and of bone health have been traced to high POP levels in grey seals (**Figure 10**). In Dutch and Belgian colonies of common tern, eggs with higher concentrations of POPs took longer to hatch, and the chicks were smaller in size. Especially in the United Kingdom, but also in other countries, fish have been widely affected by estrogens and anti-androgens in municipal wastewaters. In male fish, increased levels of the female egg yolk proteins and the occurrence of eggs in the testes have been the consequence. The antifouling agent tributyltin in ship paints has disrupted mollusc sexual development worldwide (**Figure 11**). By the 1970s, many populations of species, such as the commercially important oyster, had collapsed in heavily polluted areas. Reductions in use and exposure have led to a recovery of these populations.

There are important parallels between the increasing incidence of human disorders and those observed in wildlife. For example, testicular non-descent was observed in 68% of males in a population of black-tailed deer in Alaska, USA; similar trends were also observed in Montana, USA. There is recent evidence that animals living near humans also have increasing body weight. Moreover, studies of PCB-exposed wildlife have provided important information on exposure levels, early and subclinical effects and the clinical neurotoxicity of these chemicals. The mechanisms underlying the effects and the outcomes of exposures are often similar to those in humans.

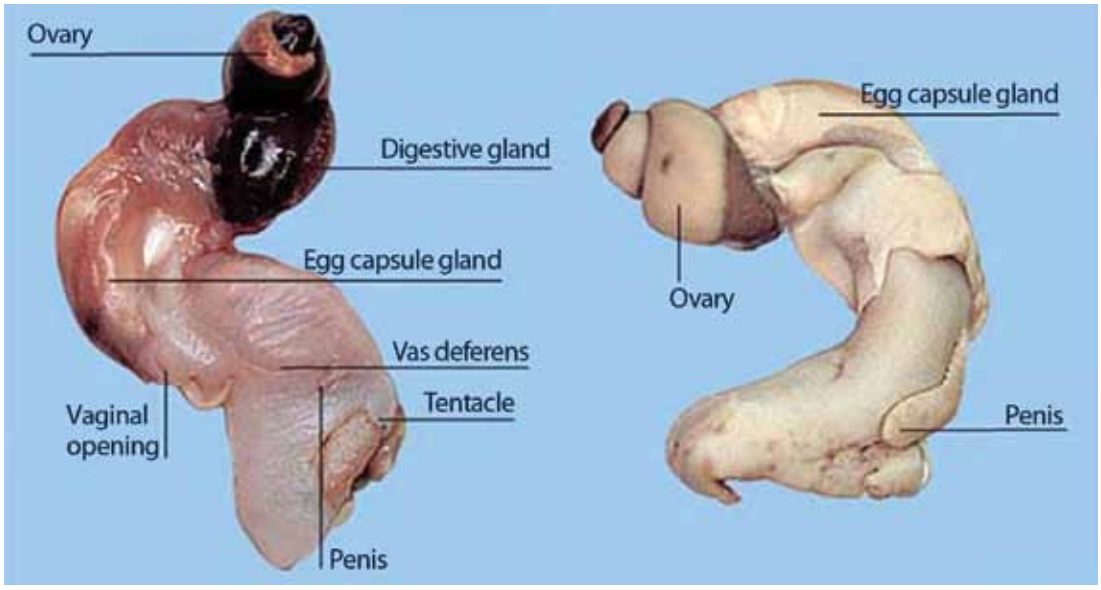


Figure 11. Common whelk (*Buccinum undatum*) showing imposex (i.e. it has both male and female genitalia).

7. Why should we be concerned?—Population effects in wildlife

- There is a worldwide loss of species or reduced population numbers of amphibians, mammals, birds, reptiles, freshwater and marine fishes (**Figure 12**) and invertebrates.
- EDCs have been shown to negatively affect body systems that are critical for the health and survival of wildlife.
- The current body burdens of POPs such as PCBs, organochlorine pesticides and methylmercury in some fish-eating birds and marine mammal populations are at levels known to cause effects on breeding and on the immune system (**Figure 13**). Some of these populations are threatened or endangered.
- Legal, technical and ethical constraints to working with wildlife, notably those listed under endangered species legislation, prevent research to investigate chemical causes of population declines in these animals.
- An increasing number of chemicals to which wildlife are exposed have been shown to interfere with the hormonal and immune systems of wildlife species. Most of these chemicals are not monitored in ecosystems. Exposed wildlife populations are often not monitored either.
- Experimental animal studies have shown that many chemicals can interfere with the development and function of endocrine systems, leading to effects on behaviour, fecundity, growth, survival and disease resistance. This increases the probability that exposure to EDCs could lead to population-level effects in wildlife.

Subtle effects of EDCs on individual animals may result in devastating effects on wildlife populations over the long term. This is hard to prove until the declines in populations are evident, at which point it may be too late to save these species.

Exposures to EDCs affect the reproductive health of wildlife species, but there have been few studies translating these effects to impacts at the population level. Notwithstanding this, higher rates of reproductive problems are found in animals with higher exposure to EDCs than in those exposed to lower concentrations. As levels of EDCs decline, some wildlife populations have shown recovery. EDCs have affected immune function, resulting in increased susceptibility to infectious diseases in vertebrates, notably marine mammals. Taken together, the evidence shows that exposure to endocrine disrupting contaminants plays a significant role in wildlife health trends.

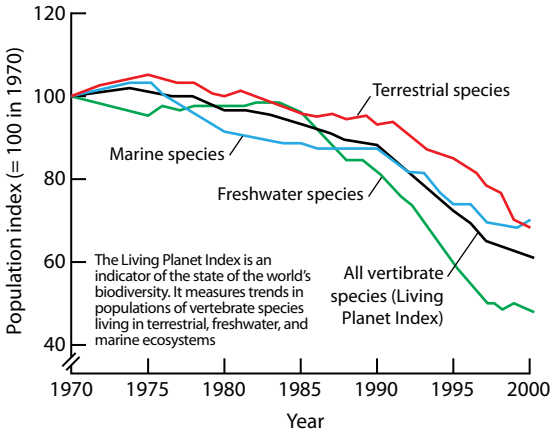


Figure 12. Population declines in wildlife (vertebrates) over 30 years, 1970–2000 (source: World Wide Fund for Nature [WWF] and the World Conservation Monitoring Centre of UNEP, used with permission).

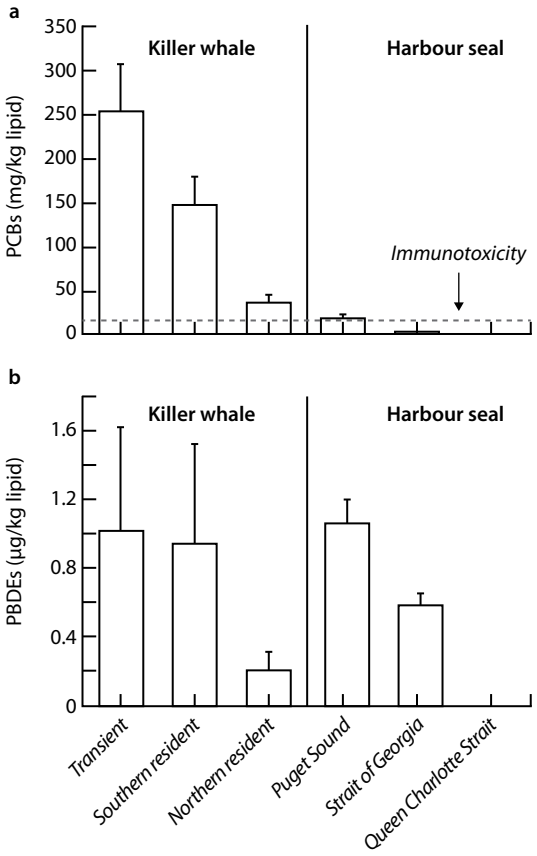


Figure 13. British Columbia's (Canada) killer whales (*Orcinus orca*) and harbour seals (*Phoca vitulina*) contain high levels of regulated PCBs and moderate levels of PBDEs. The figure was prepared using data from Krahn et al. (2007), Rayne et al. (2004) and Ross et al. (2000, 2012).

WILDLIFE ACROSS THE GLOBE DISPLAY EDC-RELATED REPRODUCTIVE EFFECTS.

8. Sensitive periods for endocrine disruptor action—Windows of exposure

Hormones and EDCs that alter hormone actions can act at all times during life—fetal development, infancy, early childhood, puberty, adulthood and old age. The timing of hormone or EDC action often determines the strength of their impact. In the adult, the hormone or EDC has an effect when it is present, but when the hormone or EDC is withdrawn, the effect diminishes—much like insulin levels rising when blood sugar is high and then declining when blood sugar declines.

In contrast, exposure to hormones or EDCs during development (in utero and infancy and early childhood in humans) can have permanent effects if the exposure occurs during the period when a specific tissue is developing. These effects may only become visible decades later. This is called developmental programming. Hormones control the normal development of tissues from the fertilized sperm and egg to the fully developed fetus. Since some tissues continue developing after birth—such as the brain and reproductive system—the sensitive period for these tissues is extended, sometimes for decades after birth.

When a tissue is developing, it is more sensitive to the action of hormones and thus EDCs.

The mechanisms by which EDC exposure during development can alter the development of specific tissues, leading to increased susceptibility to diseases later in life, are just beginning to be understood. It is clear that hormones play an important role in cell differentiation, which leads to the development of tissues and organs. Once tissues and organs are fully developed and active, then hormones have a different role: to control the integration of signals between tissues and organ systems and to maintain normal function. Early development (when hormones are controlling cell changes to form tissues and organs) is thus a very sensitive time frame for EDC action. If an EDC is present during the developmental programming of a tissue, it could disrupt the normal hormone levels, leading to changes in tissue development—changes that would be stable across the lifetime and possibly confer sensitivity to disease later in life. These effects

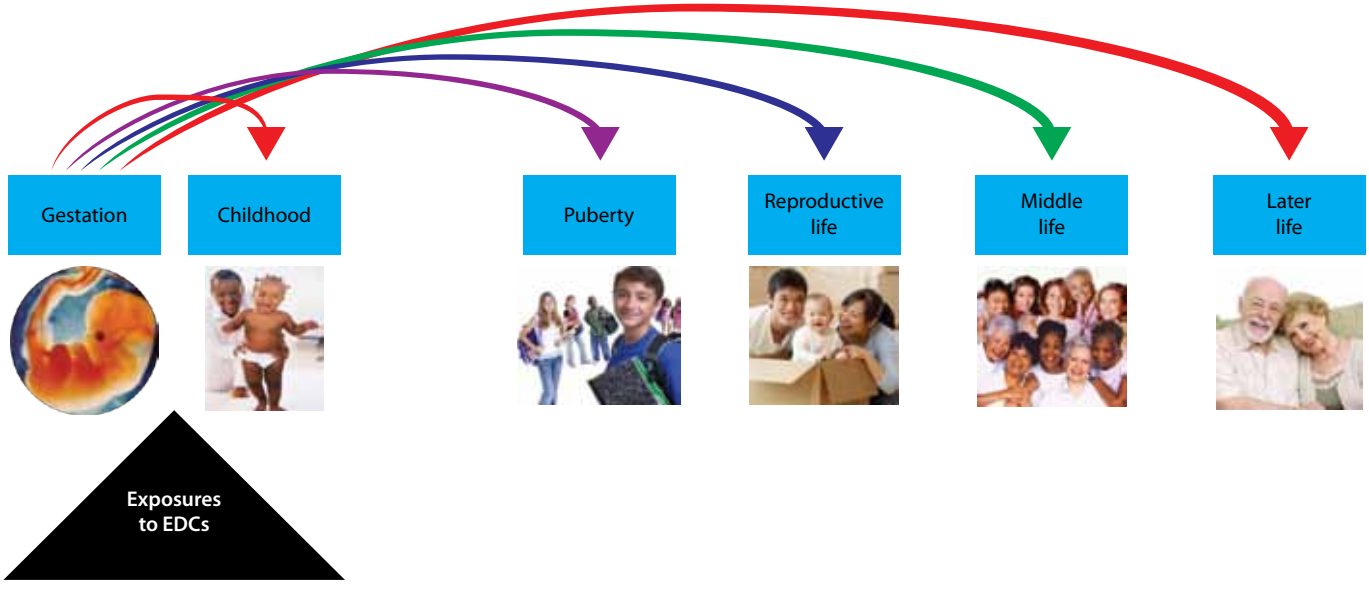


Figure 14. The effects of early exposures to EDCs may be manifested any time in life.

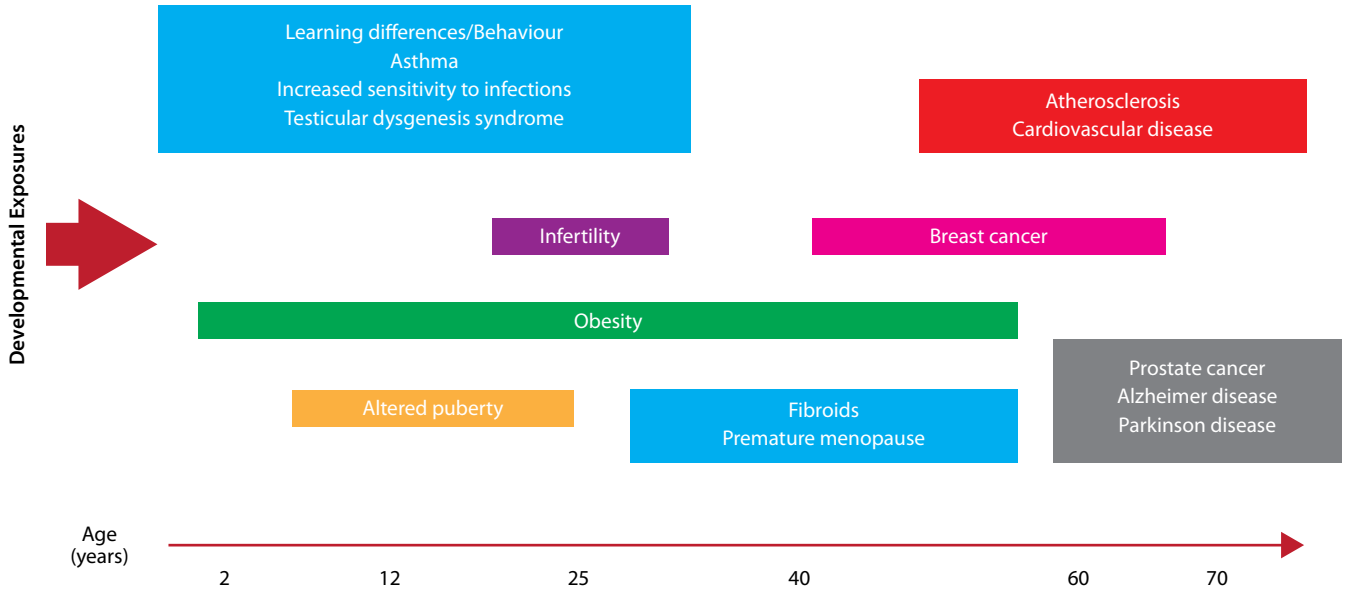


Figure 15. Examples of potential diseases and dysfunctions originating from early exposures to EDCs.

are not likely to be evident at birth, but may show up only later in life, from a few months to decades later (**Figures 14** and **15**). These developmental effects emphasize that babies and children are not just little adults!

Some EDCs produce effects that can cross generations (transgenerational effects), such that exposure of a pregnant woman or wild animal may affect not only the development of her offspring but also their offspring over several generations. This means that the increase in disease rates we are seeing today could in part be due to exposures of our grandparents to EDCs, and these effects could increase over each generation due to both transgenerational transmission of the altered programming and continued exposure across generations.

9. Occurrence of and exposures to endocrine disruptors

Since 2002, a large number of chemicals other than POPs have been identified as EDCs, and these include chemicals that have very different properties, sources and fates in the environment compared with POPs. EDCs are both man-made and natural. Some are found in a large variety of materials, products, articles and goods. They may also be by-products formed during manufacturing or combustion of wastes. These chemicals are also subjected to biological and environmental transformations that may form other EDCs. EDCs are found among many classes of chemicals, including POPs, current-use pesticides, phytoestrogens, metals, active ingredients in pharmaceuticals, and additives or contaminants in food, personal care products, cosmetics, plastics, textiles and construction materials. Once released into the environment, the more persistent chemicals can be carried by air and water currents to remote locations, and many can be biomagnified through food webs to high levels in humans and other top predators. Other chemicals have shorter lifespans in the environment but are regularly released in effluents, in agricultural runoff or from urban environments, resulting in high environmental levels near the sources (**Figure 16**).

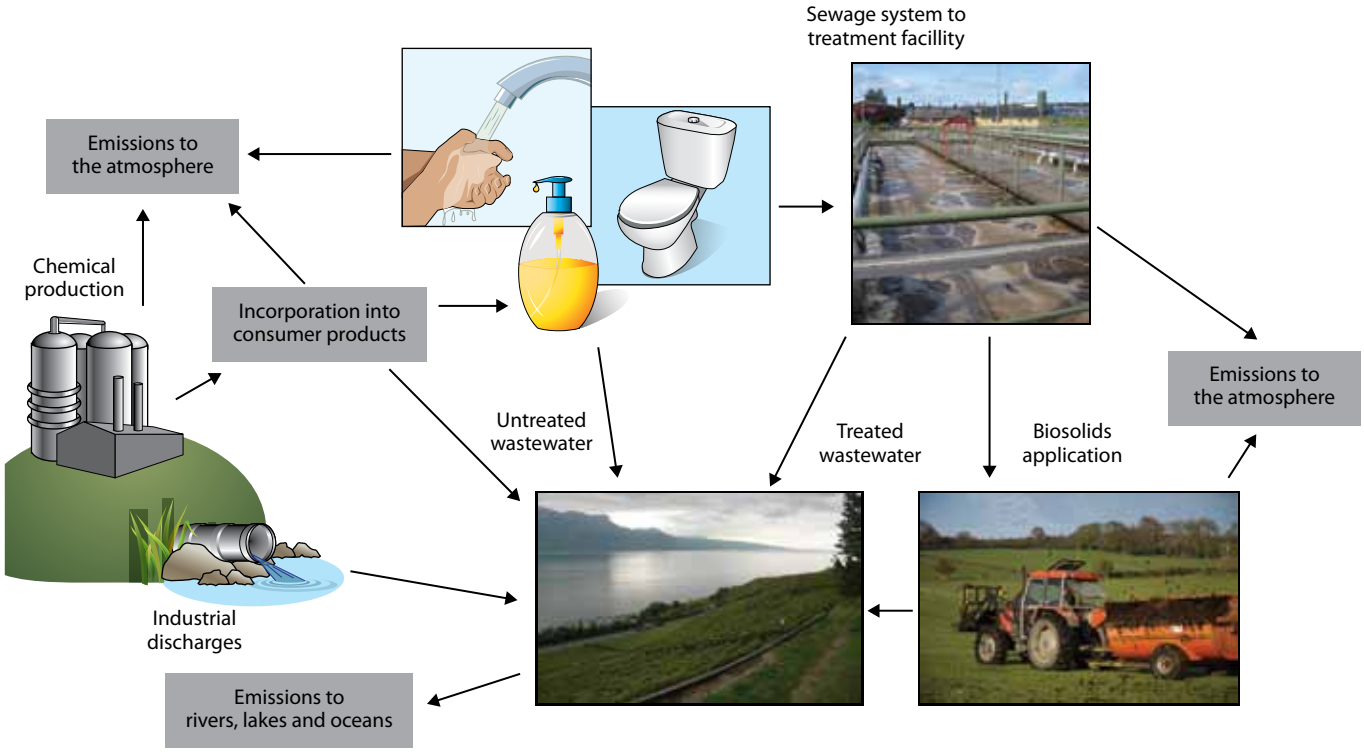


Figure 16. EDCs find their way into the environment via point and diffuse sources, as illustrated here.

Wildlife and humans are exposed to EDCs in several different ways. Air, water, soil, sediment and food are sources of EDCs for wildlife. Human exposure to EDCs occurs via ingestion of food, dust and water, via inhalation of gases and particles in the air and through dermal uptake (**Figure 17**). Transfer of EDCs from the pregnant female to the developing fetus through the placenta and to offspring in mothers' milk also occurs in both wildlife and humans. Children can have higher exposures to EDCs because of their hand-to-mouth activities. These multiple routes of exposure to a variety of EDCs mean that humans and wildlife are exposed to complex mixtures of EDCs. At this time, there are no data showing how exposure to mixtures of virtually hundreds of EDCs at low concentrations will affect human and wildlife health. However, animal studies show that exposures to mixtures of EDCs produce additive effects. These additive effects occur even when each chemical is present at low levels not shown to produce effects individually. This means that many chemicals, each at levels without individual effect, could act together to cause health problems.

Several hundred environmental pollutants have been measured in humans and wildlife around the world, even in remote places such as the Arctic. Levels of EDCs in humans and wildlife vary with their location; some are higher in people and wildlife in urban or highly industrialized areas or sites where, for example, disposal of e-waste occurs, whereas others are higher in remote environments because of long-range

Figure 17. EDCs from multiple sources can be taken up by humans by several routes, entering the body via ingestion, inhalation and skin uptake.

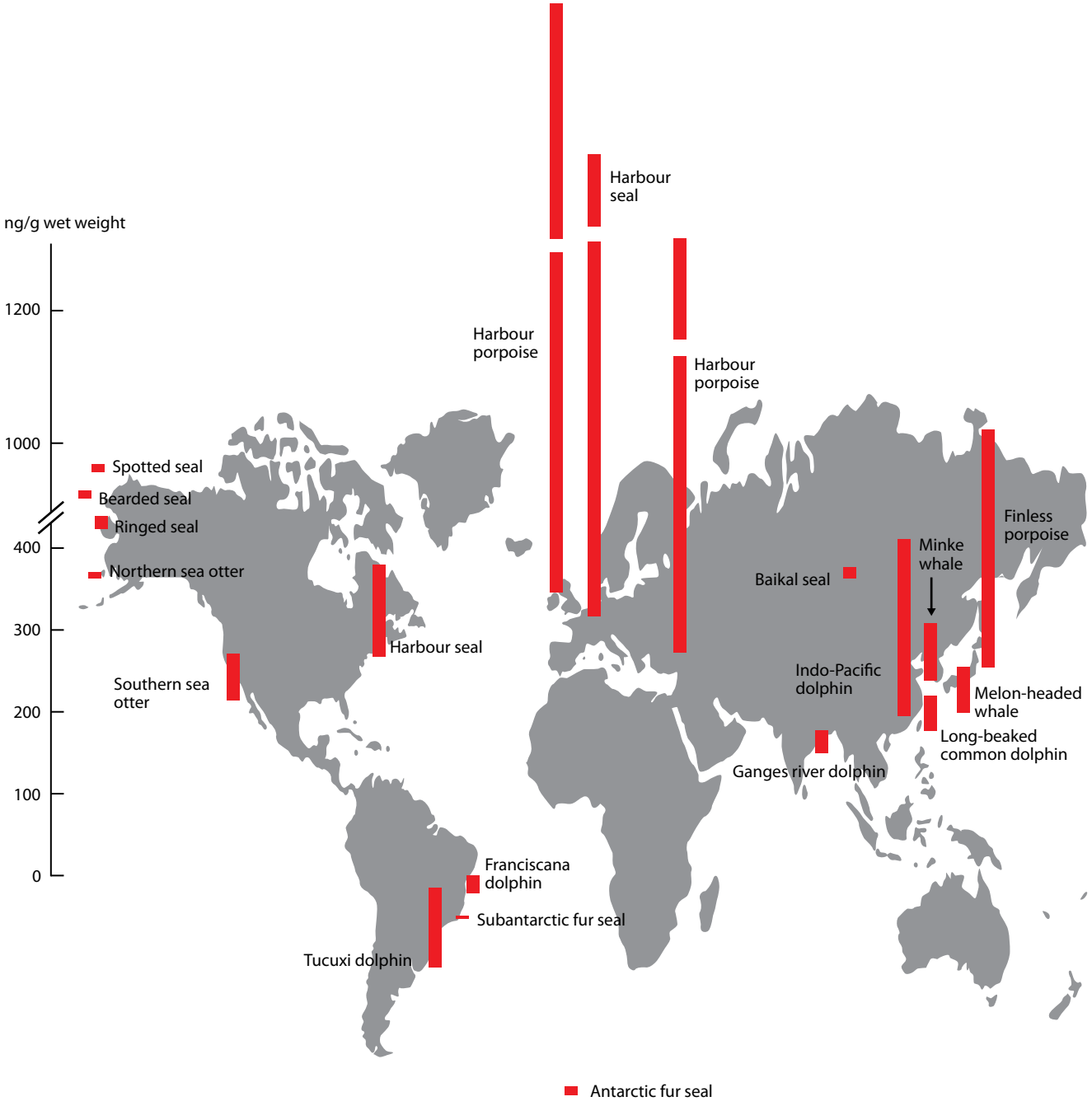


Figure 18. EDCs are found in wildlife worldwide. This figure shows concentrations (in ng/g wet weight) of perfluorooctane sulfonate, also known as PFOS, in liver of marine mammals (modified from Houde et al., 2011).

transport by air and ocean currents and food web accumulation. A few examples of exposure of wildlife around the world are shown in **Figures 18** and **19**. There are no longer any pristine areas without environmental pollutants. In addition, levels of chemicals in the body are tightly linked to trends in their use. There are good examples where bans or reductions in chemical use have resulted in reduced levels in humans and wildlife. Indeed, human and animal tissue concentrations of many POPs have declined because the chemicals are being phased out following global bans on their use. In contrast, EDCs that are being used more now are found at higher levels in humans and wildlife. It is notable how well production and exposure mirror each other, as exemplified in **Figure 20**.

Hundreds of chemicals in commerce are known to have endocrine disrupting effects. However, thousands of other chemicals with potential endocrine effects have not been looked for or tested. It is likely that these chemicals are contributing to wildlife and human exposures to EDCs. The situation is illustrated in **Figure 21**. Since only a very limited number of all chemicals in commerce have been tested for their endocrine disrupting properties, there may be many more with such properties. Also, the EDC metabolites or environmental transformation products and the by-products and products formed upon waste treatment are not included in these estimates, and their endocrine disrupting effects are mainly unknown.

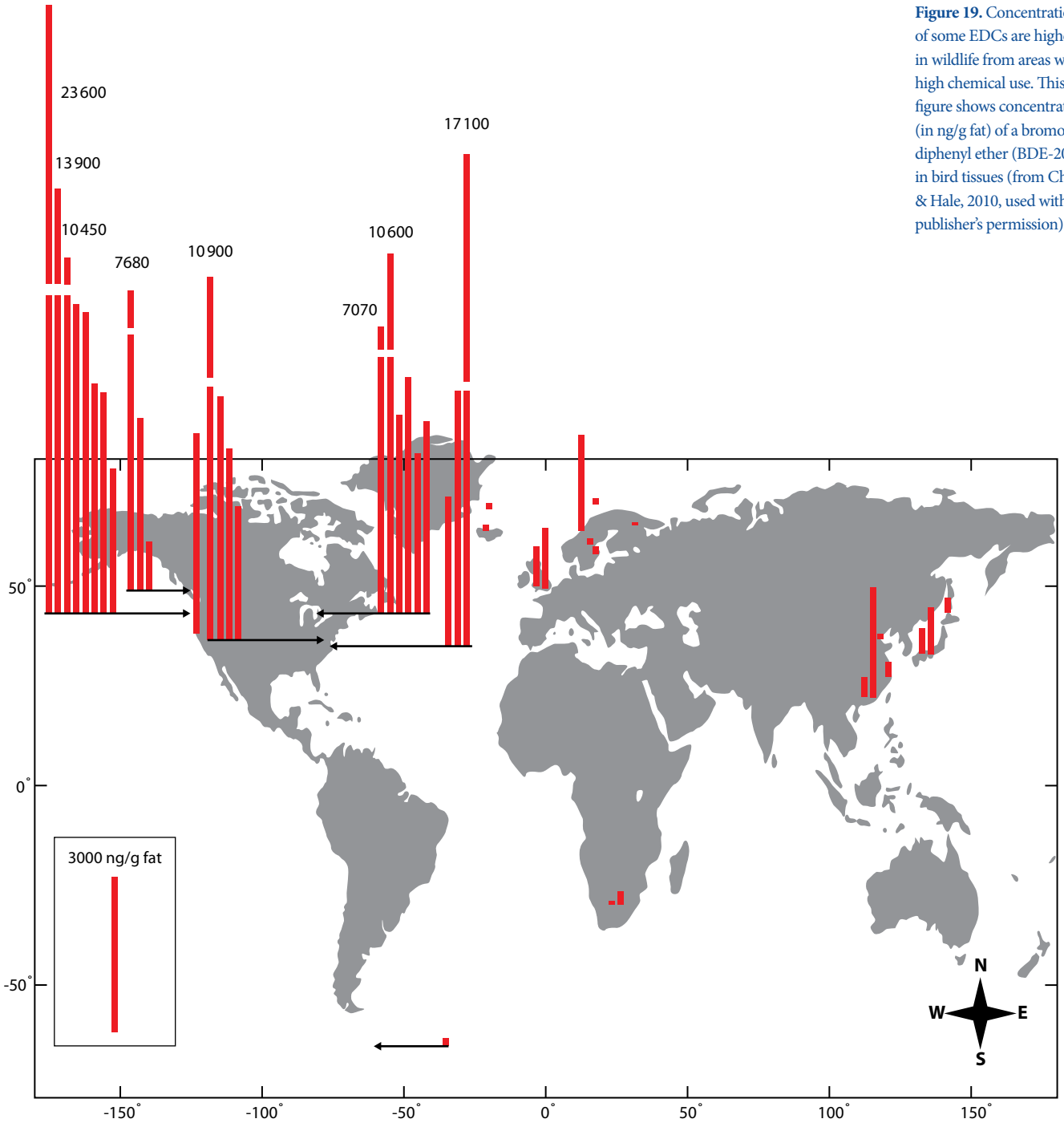
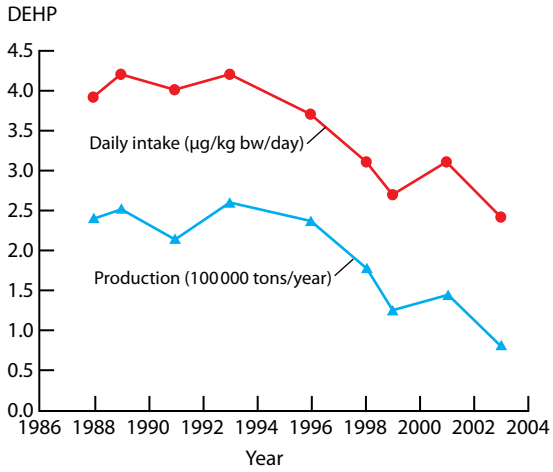


Figure 19. Concentrations of some EDCs are highest in wildlife from areas with high chemical use. This figure shows concentrations (in ng/g fat) of a bromo-diphenyl ether (BDE-209) in bird tissues (from Chen & Hale, 2010, used with publisher's permission).



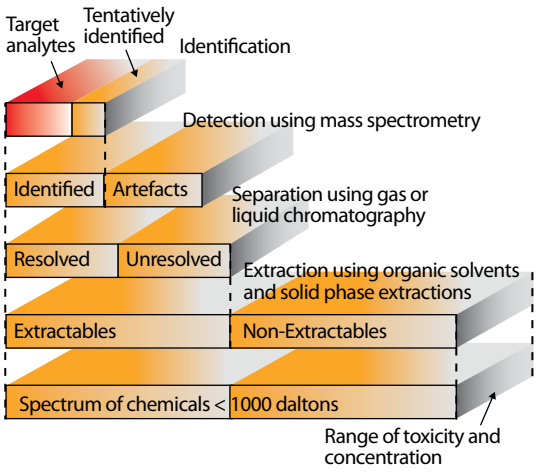


Figure 20. (left) Time course of industrial di(2-ethylhexyl)phthalate (DEHP) production in Germany, and median daily intake of DEHP in university students (from Helm, 2007, used with publisher's permission).

Figure 21. (right) An illustration of the complexity of measuring chemicals, including potential EDCs, in environmental media.

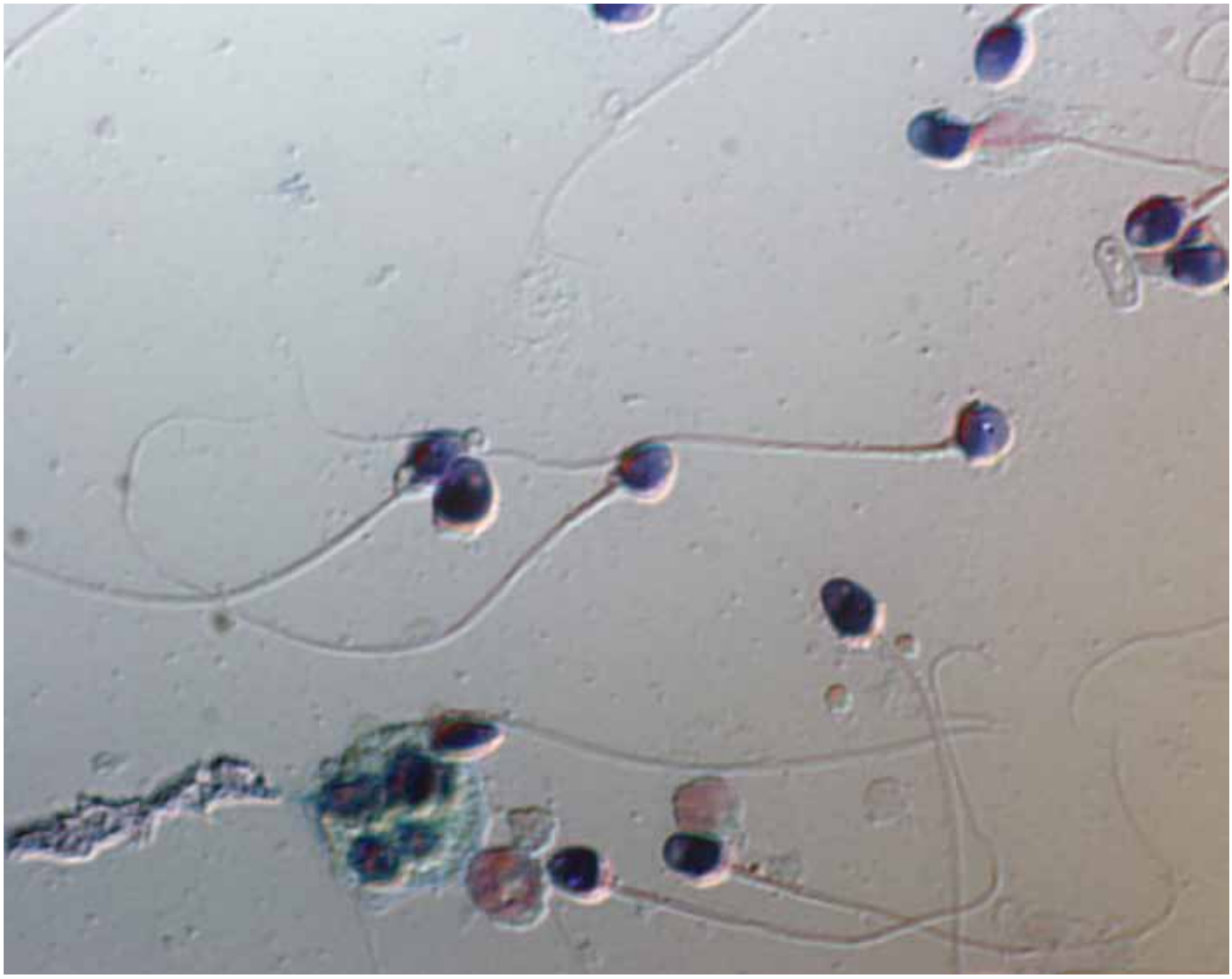
10. The tip of the iceberg

Because only a small fraction of the hundreds of thousands of synthetic chemicals in existence have been assessed for endocrine disrupting activity, and because many chemicals in consumer products are not identified by the manufacturer, we have only looked at the "tip of the iceberg". How many EDCs are there? Where do they come from? What are the human and wildlife exposures? What are their effects individually and in mixtures during development and adulthood and even across generations? What are their mechanisms of action? How can testing for EDCs be improved? All of these questions need answers.

11. Testing for EDCs

Since there are data from epidemiological studies showing associations between human disease end-points and EDC exposures, it is likely that endocrine diseases and disorders are occurring at current exposure levels. Put another way, this means that there are situations in which individually safe exposures of EDCs have reached a collectively harmful level or in which levels thought to be safe are not so.

When chemicals are tested for endocrine disrupting activity under specific validated guideline studies, it is customary to examine three doses to determine a level not apparently associated with observable effects. This level, termed the no-observed-adverse-effect level, is then divided by a so-called safety or uncertainty factor (of 100, for example) to extrapolate to levels expected to be safe for humans or wildlife. The doses declared safe are not actually tested, nor are the mixtures. These studies also assume that there is a threshold for EDC effects, that there will be no effects at low doses and that the dose–response curve rises with increasing dose. As noted above, there is no threshold for EDC effects due to the presence of active hormone pathways, and EDCs are likely to have effects at low doses. Consequently, their dose–response curves will not necessarily rise in proportion to dose. Regulatory guideline studies also focus on histopathology and organ and body weights as the end-points. As noted above, EDCs can cause many diseases and affect many disease end-points that are not currently assessed in regulatory studies. Also, risk assessment approaches do not always assess toxicity during development, which is the most sensitive window for EDC action, and also do not follow the animals for their lifetime, which is needed to assess resulting diseases.



12. Lessons from the past

How can society protect our health and that of future generations from the actions of EDCs? What can we learn from the past that will help us?

One option is to ban a chemical shown to cause toxicity and disease. Over the last 40 years, only a handful of chemicals—e.g. lead, POPs, tributyltin, di(2-ethylhexyl)phthalate, nonylphenol and chlorpyrifos—have been banned in many countries, and sometimes these bans concern specific uses only. Nonetheless, there have been clear benefits for human and wildlife health from the declining use of these chemicals.

One of the best examples of positive action is the banning of residential use of the organophosphate insecticide chlorpyrifos in the USA in 2000. Chlorpyrifos has been shown to be a potent neurotoxicant, causing developmental delays, attention problems and ADHD in children. Today, the manufacturer in question has phased out products for residential uses around the world; the chemical is still used professionally worldwide as an insecticide on fruits and vegetables in commercial agriculture. Following the residential ban in the USA, children's blood levels in New York declined significantly within one year and were reduced to less than half within two years.

Tributyltin is particularly interesting, as it was banned from use on ship hulls due to its reproductive effects on molluscs. In harbours where tributyltin use has declined, environmental levels have decreased, and so too have the effects of this EDC on the wildlife living in these areas. However, organotins are still used as fungicides on numerous plants and as components in polyvinyl chloride plastic.

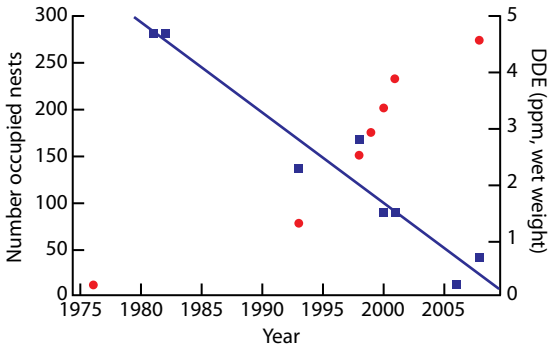


Figure 22. Wildlife populations affected by EDCs can recover after a ban of the chemical. This figure shows declining DDE ("blue square") concentrations (in parts per million wet weight) in osprey eggs in relation to the number of osprey nests occupied ("red dot") in Oregon, USA (based on data in Henny et al., 2010).

POPs such as PCBs and DDT were banned in many countries over 20 years ago due to their environmental persistence and toxicity. As a result, their levels in humans and wildlife have declined in recent decades. Bird populations exposed to high levels of DDT, and in particular to its persistent metabolite, DDE, in the 1950s through 1970s in North America and Europe are, since 1975, showing lower concentrations of DDT and DDE and clear signs of recovery (**Figure 22**). However, there are studies showing that current low levels of these persistent chemicals are still causing harm, because they or their breakdown products remain in the environment long after their use has been banned.

Lead is an important example of the cost of inaction in the face of toxicity data. Lead has been a known neurotoxicant since the Roman times; nonetheless, it was used in gasoline and paint around the world. The impact of lead on children is profound, because it causes irreversible damage to developing bone and brain tissues. The most damaging impact resulted from the use of lead in gasoline, which caused an estimated intelligence quotient (IQ) loss of five points in millions of children worldwide.

The ban on tetraethyl lead in gasoline occurred only after decades of inaction, when substitutes were available. Following the ban in the USA, lead levels in children fell dramatically, showing that the ban had a huge impact on improving human health (**Figure 23**).

While this is an example of success, the scientific data were present many years before the policies were changed and the chemical was banned. During that time, children's health continued to be harmed. So the question is, when are there sufficient data to act? Perhaps the answer is in making more use of the precautionary principle to ban or restrict chemicals in order to reduce exposure early, even when there are significant but incomplete data and before there is significant and long-lasting harm.

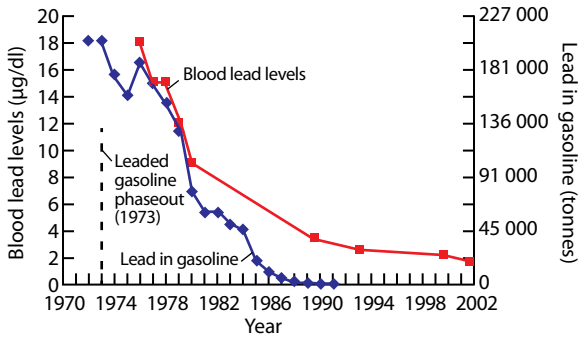


Figure 23. Ban on lead in gasoline and the impact of this decision on children's blood lead levels (based on data from the National Health and Nutrition Examination Survey in the USA).

13. Main conclusions and advances in knowledge since 2002

General aspects on endocrine disruption: Some endocrine disruptors can act directly on hormone receptors as hormone mimics or blockers. Others can act directly on any number of proteins that control the delivery of a hormone to its normal target cell or tissue. Further, the affinity of an endocrine disruptor to a hormone receptor is not equivalent to its potency, and the chemical potency on a hormone system is dependent upon many factors. Also, endocrine disruption represents a special form of toxicity, and this must be taken into consideration when interpreting the results of studies of EDCs or when designing studies to clarify the effects of EDCs and quantifying the risks to human and wildlife health.

Environmental chemicals can exert endocrine disrupting activity on more than just estrogen, androgen and thyroid hormone action. Some are known to interact with multiple hormone receptors simultaneously. Sensitivity to endocrine disruption is highest during tissue development; developmental effects will occur at lower doses than are required for effects in adults. Hence, testing for endocrine disruption must encompass the developmental period and include lifelong follow-up to assess latent effects.

Over the last 10 years, it has been established that endocrine disruptors can work together to produce additive effects, even when combined at low doses that individually do not produce observable effects. It has also become evident that endocrine disruptors may produce non-linear dose–response curves both in vitro and in vivo, by a variety of mechanisms.

Female reproductive health: Animal studies have shown that EDC exposures during early development can cause altered mammary gland and uterine development, accelerated or delayed puberty in females, disruption of fertility cycles, fibroids and endometriosis-like symptoms. These effects are similar to those seen in human populations, and it is reasonable to suspect that EDCs are adversely affecting human female reproductive health. Few studies have explored the role of EDCs and potential EDCs in causing female reproductive health disorders. Most of the available evidence comes from studies of adults rather than babies or children and often from exposures to POPs. Understanding of the contribution from more modern chemicals has only recently expanded.

There is much conflicting epidemiological evidence regarding the involvement of EDCs in premature puberty and breast development, menstrual cycles and adverse pregnancy outcomes (including preterm birth) in women. This is hardly surprising, considering the complexity of relating exposure measures to health outcomes relative to the timing and duration of exposures and including confounding factors such as maternal age and weight and the quality of prenatal care. There has been insufficient study of the relationship between EDC exposures and polycystic ovarian syndrome or fibroids in women. Limited data link phthalate exposures with increased fibroid prevalence. A number of studies have examined associations between exposure to chemicals and endometriosis, although most have measured exposure in adult life. PCBs, dioxins and phthalates are implicated, although studies are sometimes conflicting.

Historically high incidences of fibroids have also occurred in seal populations in the Baltic Sea and have been associated with exposure to contaminants (particularly PCBs and organochlorine pesticides). Recovery of these populations is now occurring, following a decline in the concentrations of these chemicals. More evidence now exists that reduced reproductive success in female birds, fish and gastropods is related to exposure to PCBs and dioxins. As exposure to these EDCs decreased, adverse reproductive effects in wild populations also decreased.

Male reproductive health: Occupational or accidental exposure of pregnant women to estrogen (DES) or to mixtures of EDCs that interfere with male hormone action (e.g. anti-androgenic pesticides) increases the risk of testicular non-descent (cryptorchidism) in their sons, causing reduced semen quality and increased risk of subfertility and testicular cancer in adult life. No associations have been found with individual chemicals, underlining the importance of including mixtures assessment in epidemiological and laboratory investigations.

Cryptorchidism is sometimes found together with penile malformations (hypospadias). Limited evidence suggests a slightly increased risk of hypospadias or of reduced semen quality associated with exposure to mixtures of endocrine disrupting pesticides. Limited evidence also

suggests links between maternal phthalate exposure and reduced anogenital distance (a proxy for reduced semen quality) in baby boys. For most chemicals, associations between fetal exposure and childhood or adult male reproductive health have not been studied. Few data sets contain measures of chemical exposures in pregnant women and of semen quality in their adult sons 20–40 years later.

Laboratory experiments with rats and epidemiological studies strongly suggest that the co-occurrence of cryptorchidism, hypospadias, testis germ cell cancer and impaired semen quality is the result of reduced androgen action during fetal development, causing testicular dysgenesis syndrome. Using the rat model, a large and convincing body of literature shows that a wide range of anti-androgenic and estrogenic EDCs can cause testicular dysgenesis syndrome in the laboratory rat. Chemicals testing positive in this model include phthalate plasticizers and a range of anti-androgenic fungicides and pesticides. Limited evidence also exists for the painkiller paracetamol. Effects of phthalates in the rat are not seen in the mouse or in human testis ex vivo, and for bisphenol A (BPA), the human testis model is more sensitive to toxic effects than the rat model. Better models of the human testis are needed for use in chemical testing.

With the exception of testicular germ cell cancers, which are logistically difficult to detect, symptoms of androgen deficiency and estrogen exposure also occur in a variety of wildlife species in both urban and rural environments and have been associated with exposure to chemicals in a limited number of species in some areas. The feminizing effects of estrogenic chemicals from sewage effluents on male fish was first reported in the 1990s and have now been seen in many countries and in several species of fish, indicating that this is a widespread phenomenon. Feminized (intersex) male fish have reduced sperm production and reduced reproductive success. The suite of effects seen in wildlife can be reproduced in laboratory studies in which experimental animals are exposed to estrogenic and anti-androgenic EDCs.

Sex ratios: EDC-related sex ratio imbalances, resulting in fewer male offspring in humans, do exist as shown for 2,3,7,8-tetrachlorodibenzo-p-dioxin and 1,2-dibromo-3-chloropropane, although the underlying mechanisms are unknown. Also, EDC-related sex ratio imbalances have been seen in wild fish and molluscs, and the effects of EDCs on sex ratios in some of these species are also supported by laboratory evidence.

Human fertility rates: Fertility rates are declining all over the world, particularly in industrialized countries. Although today we see stable, but ageing, human populations in Japan and Europe, we shall soon see significant reductions in their populations, as their fertility rates have been below replacement levels for 20–40 years. Contraception and changes in social family structures help explain these changes, although increasing reproductive health problems among men and women may also be important factors.

Population declines in wildlife: Wildlife species and populations continue to decline worldwide due to a number of factors, including overexploitation, loss of habitat, climate change and chemical contamination. Given our understanding of EDCs and their effects on the reproductive system, it is extremely likely that declines in the numbers of some wildlife populations (raptors, seals and snails) were because of the effects of chemicals (DDT, PCBs and tributyltin, respectively) on these species. The evidence for POPs as a cause of these population declines has increased now relative to 2002, due to increases in these populations following the restrictions on the use of these chemicals. EDCs in modern commerce with mechanisms of action similar to those of POPs are suspected to also be a factor contributing to declines seen in wildlife species today. Demonstrating a clear link between endocrine effects in individuals and population declines or other effects will always be challenging, however, because of the difficulty in isolating the effects of chemicals from the effects of other stressors and ecological factors. An endocrine mechanism for current wildlife declines is probable but not proven.

Thyroid health: Epidemiological evidence suggests that several groups of common contaminants, including PCBs, brominated flame retardants, phthalates, BPA and perfluorinated chemicals, are associated with reduced serum thyroid hormone levels in humans. Moreover, a much longer list of chemicals has caused a reduction in circulating levels of thyroid hormones or interfered directly with thyroid hormone action in experimental animals. Severe thyroid hormone deficiency causes severe brain damage, such that universal screening of thyroid hormone levels in serum occurs all over the world. Moderate (25%) or even transient insufficiency of thyroid hormones during pregnancy is also associated with reduced IQ, ADHD and even autism in children and with hypothyroid disorders in adults. Moreover, reduced serum thyroid hormone levels, although

still within population ranges classified as clinically "normal", have been identified as risk factors for increased serum cholesterol and elevated blood pressure and reduced bone density in postmenopausal women and so will be useful measures to investigate the relationship between chemical exposures and disease.

Not all studies will find exactly the same relationships between exposure and disease outcomes due to the difficulties in standardizing exposure measures and levels of hormones relative to the timing and duration of exposure. For thyroid hormones, levels are so variable between individuals that multiple measures in the same individual would be required to estimate a "set point" with a precision of 5%. This known variability should be incorporated into study designs. The issue is whether the correlations between contaminant exposure and various measures of endocrine function are consistent with effects on population health that are mediated by effects on hormone action. The complexity underlying the data is interpreted by some to indicate that there is no convincing evidence that chemicals can interfere with thyroid hormone action in humans. Considering that there is strong evidence linking thyroid hormone levels with adverse outcomes, particularly in children, precautionary approaches are necessary.

There is strong evidence to conclude that thyroid hormones play the same role in brain development in both animals and humans. Therefore, rodents are useful models for testing chemicals in order to protect human populations from additional exposures. The current set of validated test methods and human clinical measures, however, considers changes in thyroid hormone levels only and needs to be improved to encompass changes in thyroid hormone action. This means that there could be inconsistent relationships between exposure to thyroid disrupting chemicals and measures of thyroid function in humans, but very strong evidence in animals indicating that chemicals can interfere with thyroid hormone action. This is certainly true for PCBs.

Evidence of relationships between exposure to chemicals and thyroid hormone disruption in wildlife species has improved in the last decade, especially in relation to exposure to the flame retardant PBDEs and PCBs, but other chemicals have been inadequately studied. The strength of evidence supporting a role for EDCs in disrupting thyroid function in wildlife adds credence to the hypothesis that this could occur in humans.

Thyroid disruption is acknowledged to be poorly addressed by the chemical tests currently listed in the Organisation for Economic Co-operation and Development (OECD) conceptual framework. Genetic lines of mice are now widely available that could help clarify the mechanisms by which chemical exposures can interfere with thyroid hormone action.

Neurodevelopment: It is not widely appreciated that hormones play many critical roles in neurodevelopment, including the neuroendocrine circuits that control sex-specific behaviour and physiology, and therefore that EDCs could cause a series of behavioural conditions and psychiatric disorders that are evident in societies. Sufficient data indicate that in utero exposure to EDCs affects cognition in animal studies, and limited data indicate that sexually dimorphic behaviours are also affected. Although some test guidelines for developmental neurotoxicity have been developed, no chemical testing strategies currently require evaluation of the ability of chemicals to produce such effects.

There are sufficient data in human populations to conclude that high exposures to thyroid disrupting PCBs during fetal development (e.g. the children whose mothers ate contaminated fish from Lake Michigan or in the Yu-Cheng, or "oil disease", children born to mothers exposed to PCBs) or to potential EDCs, such as lead and mercury, are linked to general cognitive problems and alterations in sexual behaviour. Even relatively low exposures, however, are associated with reduced cognitive function. The most consistent observations are with impaired executive functioning, followed by processing speed, verbal ability and visual recognition and memory. ADHD is overrepresented in children whose mothers had low thyroxine levels in the first trimester of pregnancy and in populations with elevated exposure to organophosphate pesticides, still found in some populations. There is almost no information concerning the effects of mixtures of neuroendocrine disruptors, even though we know that they co-exist in human tissues. Data available suggest additive effects of different chemicals.

Studies of exposed wildlife provide important information on exposure levels, early and subclinical effects and the clinical neurotoxicity of EDCs, because the mechanisms, underlying effects and outcomes of exposure are often similar to those in humans. Data showing effects on growth, development and behaviour in wildlife exist for some PCBs and mercury, but are sparse or non-existent for other EDCs.

Hormone-related cancers: Despite a great deal of research, the causes of most hormonal cancers are a mystery. It is clear that hormones are required for the growth of cancerous tissues, but their involvement in the earlier stages of carcinogenesis, through perhaps epigenetic effects, is unclear. Studies with animals now show that exposure to hormones (synthetic or natural) or EDCs (e.g. PCBs, PBDEs, dioxins, some organochlorine pesticides, BPA) during early development of some endocrine glands (e.g. breast, endometrium, prostate) can alter their development, perhaps through effects on stem cells, with possible consequences for susceptibility to cancer. In some cases, cancer has been demonstrated in these animals. In the thyroid gland, the existence of stem cells has been hypothesized, but not demonstrated. Although various chemicals have been shown to cause thyroid cancer in animals, current understanding of thyroid cancer does not link it to an endocrine mechanism.

Many poorly designed and conflicting studies have arisen, until very recently, from lack of knowledge that exposures must consider mixtures and must be measured before the cancer appears, in fetal development, in many cases. This means that, despite growing evidence that hormones are risk factors for several endocrine cancers, few epidemiological studies have shown links with EDCs. For breast cancer, the most convincing evidence appears to come from associations with EDCs devoid of estrogenic activity, such as dioxins and furans, for which sufficient evidence exists. For endometrial and ovarian cancer, very few studies have been carried out, and those that exist are conflicting. For prostate cancer, sufficient evidence exists for an association with exposures to mixtures of pesticides in agriculture and in pesticide manufacturing and to cadmium and arsenic, whereas evidence is conflicting for an association with PCB and organochlorine exposures. Many of the pesticides are acetylcholinesterase inhibitors, which also interfere with metabolic conversion of hormones. Very many chemicals have not been investigated at all. For thyroid cancer, limited studies indicate higher rates in pesticide applicators, although some of these also stem from iodine deficiencies in these people.

Similar types of cancers of the endocrine organs, particularly reproductive organs, are also found in wildlife species (several species of marine mammals and invertebrates) and in domestic pets. In wildlife, endocrine tumours tend to be more common in animals living in polluted regions than in those inhabiting more pristine environments.

There are many deficiencies in regulatory testing methodologies for EDCs. Rodent strains developed for carcinogen testing were not developed as models for the demonstration of mammary cancer; an animal mammary carcinogen may be a human carcinogen, but not necessarily with the breast as a target organ. Other rat strains not routinely used for testing would be more suitable for testing, but have hitherto been used for only a handful of chemicals.

Adrenal disorders: Numerous chemicals, mainly POPs, potentially affecting adrenal structure and function have been described using in vitro assays, but no studies have investigated EDC associations with adrenal hormone secretion in humans. Few studies have been carried out with laboratory animals. The great majority of chemicals in commerce have not been tested.

Bone disorders: It is well established that bone is a target tissue for estrogens, which affect bone mineralization and maturation. Very little evidence, however, exists for effects of EDCs on these processes, except in cases of accidental high-exposure incidents with hexachlorobenzene , PCBs and polychlorinated dibenzofurans and in people eating contaminated fish from the Baltic Sea.

Metabolic disorders: The control of metabolism involves many components of the endocrine system, including the adipose tissues, brain, skeletal muscle, liver, pancreas, thyroid gland and gastrointestinal tract. There are now animal data showing that embryonic exposure to EDCs or potential EDCs (e.g. tributyltin, BPA, some organochlorine and organophosphate pesticides, lead, perfluorooctanoic acid, phthalates) leads to altered cholesterol metabolism, possible weight gain and type 2 diabetes in adulthood. There are no compelling animal data linking chemical exposures to type 1 diabetes, although some chemicals can affect the function of insulin-producing beta cells in the pancreas, including BPA, PCBs, dioxins, arsenic and some phthalates. Many of these chemicals are also immunotoxic in animal models, and so it is plausible that they could act via both immune and endocrine mechanisms to cause type 1 diabetes. Metabolic syndrome may also result from chemical exposures, although there has been little study of this.

Limited epidemiological data exist to support the notion that EDC exposure during pregnancy can affect weight gain in infants and children. Limited epidemiological data show that adult exposures to some EDCs (mainly POPs, arsenic and BPA) are associated with type 2 diabetes, but there are

no data for type 1 diabetes, there is insufficient evidence of endocrine mechanisms and there is insufficient study of this area in general.

Immune disorders: It is increasingly clear that EDCs likely play a role in the rise in immune-related disorders in both humans and wildlife. Many immune disorders have well-established ties to the endocrine system, such that disruption of select endocrine pathways may disturb the immune response, potentially causing allergies, endometriosis, bone disorders, autoimmune thyroid disease and immune cancers. This is because the immune and endocrine systems are intricately connected through cross-talk between certain hormonal receptors and immune signalling pathways. Sufficient data now support a role for the lipid X receptor (LXR) and the steroid and xenobiotic receptor (SXR) in regulating white blood cell proliferation, and there are data linking inflammation, immune dysfunction and immune cancers with EDCs.

Several studies with animals have demonstrated activation or repression of receptor signalling pathways involved in immune–endocrine interactions by organochlorine pesticides, PCBs, organotins, alkylphenols, phthalates, atrazine and BPA. Limited experimental and epidemiological evidence suggests that some PCBs, estrogens, atrazine and phthalates are developmental immunotoxicants, causing increased risk of inflammatory and autoimmune disorders. There are strong links, supported by animal studies, between phthalate exposure and the rising incidence of asthma. Endocrine mechanisms are highly plausible, but are not always proven or investigated. Together, these new insights stress a critical need to better understand how EDCs affect normal immune function and immune disorders and how windows of exposure may affect disease incidence (particularly for childhood respiratory diseases).

Human and wildlife exposures to EDCs: There is far more knowledge on EDC exposure today than there was 10 years ago. This applies to the diversity of chemicals being implicated as EDCs and exposure routes and levels in humans and wildlife. As examples, brominated flame retardants were mentioned only briefly and perfluorinated compounds not at all when the IPCS document on EDCs was prepared 10 years ago (IPCS, 2002). In addition to these, there are now many more EDCs being found in both humans and wildlife. The most relevant main messages regarding exposure to EDCs are summarized below.

Unlike 10 years ago, it is now better understood that humans and wildlife are exposed to far more EDCs than just POPs. EDCs are chemically diverse, are primarily man-made chemicals and are used in a wide range of materials and goods. EDCs are present in food, nature (wildlife) and human beings. They can also be formed as breakdown products from other anthropogenic chemicals in the environment and in humans, wildlife and plants. Humans and wildlife are exposed to multiple EDCs at the same time, and there is justifiable concern that different EDCs can act together and result in an increased risk of adverse effects on human and wildlife health. Exposures to EDCs occur during vulnerable periods of human and wildlife development—from fertilization through fetal development and through nursing of young offspring—which raises particular concern. Children can have higher exposures due to their hand-to-mouth activities and higher metabolic rate.

Right now, only a narrow spectrum of chemicals and a few classes of EDCs are measured, making up the "tip of the iceberg". More comprehensive assessments of human and wildlife exposures to diverse mixtures of EDCs are needed. It should be a global priority to develop the capacities to measure any potential EDCs. Ideally, an "exposome", or a highly detailed map of environmental exposures that might occur throughout a lifetime, should be developed. New sources of exposure to EDCs, in addition to food, have been identified and include indoor environments and electronics recycling and dumpsites (the latter being issues of particular concern for developing countries and countries with economics in transition). Not all sources of exposure to EDCs are known because of the lack of chemical constituent declarations for materials and goods.

There is global transport of EDCs through natural processes (ocean and air currents) as well as through commerce, leading to worldwide exposure of humans and wildlife to EDCs. Spatial and temporal monitoring is critical for understanding trends and levels of exposure. This monitoring should include tissues from both humans and wildlife (representing a range of species) as well as water or other environmental compartments to capture the less persistent EDCs. Levels in humans and wildlife are related to how much a chemical is used. Bans on several POPs have led to declines in environmental levels and human body burdens. In contrast, there are increasing levels of some newer EDCs, such as perfluorinated alkyl compounds and replacements for banned brominated flame retardants.

14. Concluding remarks

EDCs have the capacity to interfere with tissue and organ development and function, and therefore they may alter susceptibility to different types of diseases throughout life. This is a global threat that needs to be resolved.

Progress

We are starting to understand that a large number of non-communicable diseases have their origin during development and that environmental factors interact with our genetic background to increase susceptibility to a variety of diseases and disorders. It is also clear that one of the important environmental risk factors for endocrine disease is exposure to EDCs during development. It is also clear from human studies that we are exposed to perhaps hundreds of environmental chemicals at any one time. It is now virtually impossible to examine an unexposed population around the globe. Trends indicate an increasing burden of certain endocrine diseases across the globe in which EDCs are likely playing an important role, and future generations may also be affected.

The advances in our understanding of EDCs have been based mainly on information derived from studies in developed regions. As in 2002, there is still a major lack of data from large parts of the world, in particular from Africa, Asia and Central and South America.

Future needs

Better information on how and when EDCs act is needed to reduce exposures during development and prevent disease from occurring. A clear example of the success of primary prevention through exposure control is lead. We have identified the following needs to take advantage of current knowledge to improve human and wildlife health by prevention of environmentally induced diseases.

A. Strengthening knowledge of EDCs: It is critical to move beyond the piecemeal, one chemical at a time, one disease at a time, one dose approach currently used by scientists studying animal models, humans or wildlife. Understanding the effects of the mixtures of chemicals to which humans and wildlife are exposed is increasingly important. Assessment of EDC action by scientists needs to take into account the characteristics of the endocrine system that are being disrupted, including tissue specificity and sensitive windows of exposure across the lifespan. While there are different perspectives on the importance of low-dose effects and non-monotonic dose–response curves for EDCs, this issue is important in determining whether current testing protocols are sufficient to identify EDCs. Interdisciplinary efforts that combine knowledge from wildlife, experimental animal and human studies are needed to provide a more holistic approach for identifying the chemicals that are responsible for the increased incidence of endocrine-related disease and dysfunction. The known EDCs may not be representative of the full range of relevant molecular structures and properties due to a far too narrow focus on halogenated chemicals for many exposure assessments and testing for endocrine disrupting effects. Thus, research is needed to identify other possible EDCs. Endocrine disruption is no longer limited to estrogenic, androgenic and thyroid pathways. Chemicals also interfere with metabolism, fat storage, bone development and the immune system, and this suggests that all endocrine systems can and will be affected by EDCs. Together, these new insights stress a critical need to acquire a better understanding of the endocrine system to determine how EDCs affect normal endocrine function, how windows of exposure may affect disease incidence (particularly for childhood respiratory diseases) and how these effects may be passed on to generations to come.

Furthermore, new approaches are needed to examine the effects of mixtures of endocrine disruptors on disease susceptibility and etiology, as examination of one endocrine disruptor at a time is likely to underestimate the combined risk from simultaneous exposure to multiple endocrine disruptors. Assessment of human health effects due to EDCs needs to include the effects of exposure to chemical mixtures on a single disease as well as the effects of exposure to a single chemical on multiple diseases. Since human studies, while important, cannot show cause and effect, it is critical to develop cause and effect data in animals to support the studies on humans.

B. Improved testing for EDCs: Validated screening and testing systems have been developed by a number of governments, and it requires considerable time and effort to ensure that these systems function properly. These systems include both in vitro and in vivo end-points and various species, including fish, amphibians and mammals. New approaches are also being explored whereby large batteries of high-throughput in vitro tests are being investigated for their ability to predict toxicity, the results of which may be used in hazard identification and potentially risk assessment. These new approaches are important as one considers the number of chemicals for which there is no information, and these high-throughput assays may provide important, albeit incomplete, information. An additional challenge to moving forward is that EDC research over the past decade has

revealed the complex interactions of some chemicals with endocrine systems, which may escape detection in current validated test systems. Finally, it will be important to develop weight-of-evidence approaches that allow effective consideration of research from all levels—from in vitro mechanistic data to human epidemiological data.

C. Reducing exposures and thereby vulnerability to disease: It is imperative that we know the nature of EDCs to which humans and wildlife are exposed, together with information about their concentrations in blood, placenta, amniotic fluid and other tissues, across lifespans, sexes, ethnicities (or species of wildlife) and regions. Many information gaps currently exist with regard to what is found in human and wildlife tissues, more so for developing countries and countries with economies in transition and for chemicals that are less bioaccumulative in the body. Long-term records to help us understand changes in exposures exist only for POPs and only for a few countries.

In addition, there is a need to continue expanding the list of chemicals currently examined to include those contained in materials and goods as well as chemical by-products; it is impossible to assess exposure without knowing the chemicals to target. The comprehensive measurement of all exposure events during a lifetime is needed, as opposed to biomonitoring at specific time points, and this requires longitudinal sampling, particularly during critical life stages, such as fetal development, early childhood and the reproductive years.

Wildlife and humans are exposed to a wide variety of EDCs that differ greatly in their physical and chemical properties. Further, these compounds are generally present at trace concentrations and in complex matrices requiring highly selective and sensitive analytical methods for their measurement. The wide range of different compound classes requires a variety of analytical approaches and techniques, making it challenging to understand all of the different chemicals in the environment and in human and wildlife tissues. There is a growing need to develop new analytical techniques and approaches to prioritize the assessment of EDCs. There is global transport of EDCs through natural processes (ocean and air currents) as well as commerce, leading to worldwide exposures. New sources of exposure to EDCs, in addition to food, have been identified and include indoor environments and electronics recycling and dumpsites (of particular concern in developing countries and countries with economies in transition). The sources and routes of exposure to EDCs need to be further investigated.

D. Identifying endocrine active chemicals: Identifying chemicals with endocrine disrupting potential among all of the chemicals used and released worldwide is a major challenge, and it is likely that we are currently assessing only the "tip of the iceberg". It is possible to trace high production volume chemicals, but that is not the case for the numerous additives and process chemicals. Adding greatly to the complexity, and to the number of chemicals in our environment, are the unknown or unintended by-products that are formed during chemical manufacturing, during combustion processes and via environmental transformations. While the active ingredients in pharmaceuticals and pesticides have to be documented on the final product, this is not the case for chemicals in articles, materials and goods. Personal hygiene products and cosmetics require declarations of the ingredients, and the number of chemicals applied in this sphere of uses counts in the thousands. Many sources of EDCs are not known because of a lack of chemical constituent declarations in products, materials and goods. We need to know where the exposures are coming from.

E. Creating enabling environments for scientific advances, innovation and disease prevention: Exposure to EDCs and their effects on human and wildlife health are a global problem that will require global solutions. More programmes are needed that foster collaboration and data sharing among scientists and between governmental agencies and countries. To protect human health from the combined effects of exposures to EDCs, poor nutrition and poor living conditions, there is a need to develop programmes and collaborations among developed and developing countries and those in economic transition. There is also a need to stimulate new adaptive approaches that break down institutional and traditional scientific barriers and stimulate interdisciplinary and multidisciplinary team science.

F. Methods for evaluating evidence: There is currently no widely agreed system for evaluating the strength of evidence of associations between exposures to chemicals (including EDCs) and adverse health outcomes. A transparent methodology is also missing. The need for developing better approaches for evaluating the strength of evidence, together with improved methods of risk assessment, is widely recognized. Methods for synthesizing the science into evidence-based decisions have been developed and validated in clinical arenas. However, due to differences between environmental and clinical health sciences, the evidence base and decision context of these methods are not applicable to exposures to environmental contaminants, including EDCs. To meet this challenge, it will be necessary to exploit new methodological approaches. It is essential to evaluate associations between EDC exposures and health outcomes by further developing methods for which proof of concept is currently under development.

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